BMJ Open

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014736
Article Type:	Protocol
Date Submitted by the Author:	17-Oct-2016
Complete List of Authors:	Schwingshackl, Lukas Chaimani, Anna; Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina Hoffmann, Georg; Department of Nutritional Sciences, University of Vienna Schwedhelm, Carolina; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE) Boeing, Heiner; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE)
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, NUTRITION & DIETETICS, PREVENTIVE MEDICINE

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: a systematic review and network meta-analysis

Lukas Schwingshackl[1], Anna Chaimani[2], Georg Hoffmann[3], Carolina Schwedhelm[1], Heiner Boeing[1]

[1] German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

[2] Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina, 45110 Ioannina, Greece

[3] Department of Nutritional Sciences, University of Vienna, Althanstraße 14, 1090 Vienna, Austria

Corresponding author: Lukas Schwingshackl, PhD
Arthur-Scheunert-Allee 114-116; 14558 Nuthetal, Germany
T: +49 (0)33200 88-2712
lukas.schwingshackl@dife.de

Email: anna.chaimani@gmail.com
georg.hoffmann@univie.ac.at
carolina.schwedhelm@dife.de
boeing@dife.de

Abstract

Introduction: Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association all patients with hypertension should adopt the following dietary advices: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction. The aim of the present study is to assess the efficacy of different dietary approaches on systolic and diastolic blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and Analysis: We will conduct searches in Cochrane Central Register of Controlled Trials in the Cochrane Library, PubMed, and google scholar until November 2016. Citations, abstracts, and relevant papers will be screened for eligibility by two reviewers independently. Randomized controlled trials will be included if they meet the following criteria: (1) hypertension (as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) or high normal blood pressure (mean systolic blood pressure: ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), (2) years of age: ≥18, (3) Intervention diets (different type of dietary approaches: e.g. Dietary Approach to Stop Hypertension diet; Mediterranean diet, Vegetarian diet, Paleolithic diet, low sodium diet) either hypo, iso-caloric or ad libitum diets, (4) intervention period ≥12 weeks. For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values (or change scores). Subgroup analyses are planned for: hypertensive status, study length, sample size, age, sex.

Ethics and Dissemination: As this study is based solely on the published literature, no ethics approval is required. We will publish our network meta-analysis in a peer-reviewed scientific journal.

Systematic Review Registration: PROSPERO: CRD42016049243

Keywords: diet, hypertension, blood pressure, network meta-analysis, evidence synthesis

Strengths and limitations of this study

- The protocol addresses the important question which dietary approach offers the most benefits in the management of elevated blood pressure
- The present network meta-analysis has a clearly established aim and, stringent inclusion criteria, state of the art methods for data collection and quantitative and qualitative synthesis.
- Limitations include adherence to dietary protocols, and lack of blinding across the included intervention trials

Background

Due to its frequent occurence and high impact on the development of cardiovascular and kidney disease, hypertension is one of the most challenging problems adversely affecting public-health worldwide [1]. The prevalence of hypertension accounts to nearly 40% of people older than 25 years worldwide, and the number or patients has increased from 600 million to a billion in 2008 [2].

Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association and the European Society of Cardiology and Hypertension all patients with hypertension should follow dietary modifications: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction [3, 4].

Accumulating evidence indicates that dietary factors have a predominant role in the management of elevated blood pressure [5]. In individuals without hypertension, dietary changes reduce blood pressure and prevent hypertension, thereby lowering the risk of blood pressure related complications. Epidemiological studies suggest that even slight reductions in blood pressure will reduce the risk of cardiovascular disease [6, 7].

Whereas its already well established that aerobic exercise is more effective in reducing blood pressure in hypertensive patients compared to resistance training [8], the question regarding the most effective dietary approach in the treatment of hypertension and high normal pressure has not been evaluated.

To our knowledge, up to date no systematic review and network meta-analysis has been conducted to compare different dietary modifications in the management of hypertension and high normal blood pressure. Some pairwise meta-analyses have been published comparing i.e. DASH dietary approaches [9], combined dietary approaches [10], and lower sodium intake vs usual care/control diet [11]. One of the most important questions that remain to be answered

is which dietary approach offers the most benefits in the management of elevated blood pressure.

Therefore, our aim is to compare the efficacy of different dietary approaches on blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomised trials.

Methods and design

The review was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42016049243). The present systematic review protocol was planned, conducted, and reported in adherence to standards of quality for reporting systematic review and network meta-analysis protocols [12-15] (additional file 1).

Eligibility criteria

Studies will be included in the meta-analysis if they meet all of the following criteria:

Types of studies

Randomized (controlled) design comparison between different dietary approaches (e.g. Dietary Approach to Stop Hypertension; Mediterranean diet; Vegetarian diet; Palaeolithic diet; low sodium diet; low fat diet; low carbohydrate diet; high protein diet; low glycaemic index/load diet) with a minimum intervention period of 3 months according to recent Cochrane Reviews on diet and cardiovascular risk [16, 17].

Types of participants

We will consider only adults with a mean age ≥18 years. Hypertension was defined according to the European Society of Cardiology and European Society of Cardiology & Hypertension as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure. Moreover, all patients taking antihypertensive medication will be included [18].

High normal blood pressure (mean systolic blood pressure ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), was also defined according to the European Society of Cardiology & Hypertension and the recently published SPRINT trial [18, 19]. Including patients with “high normal” blood pressure is of major relevance since is part of the metabolic syndrome diagnosis criteria [20].

Types of Interventions

Accumulating evidence indicates that dietary factors play an important role in the treatment of elevated blood pressure. Likewise, dietary modifications decrease blood pressure [21] and reduce the risk of hypertension in people without established high blood pressure [22]. Even if modest, a reduction in blood pressure can have an important impact on health of entire populations [5]. We will take into account all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control diet or another intervention diet.

Eligible types of dietary approaches will be, e.g.:

- Dietary Approach to Stop Hypertension (DASH): high intake of fruits & vegetables, low-fat dairy, whole grain [21]
- Mediterranean dietary pattern: olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals [23]
- Low carbohydrate diet (<30% carbohydrates of total energy intake, high intakes of animal high in animal or/and plant protein) [24]
- High protein diet [25] (≥ 25% protein of total energy intake)
- Low fat diet (<30% carbohydrates of total energy intake, high in grains and cereals) [24, 26]
- Vegetarian diet (no meat and fish) [27]
- Palaeolithic diet (lean meat, fish, eggs, vegetables, fruits, berries, and nuts; Dairy products, cereals, added salt, and refined fats and sugar were excluded) [28]
- Low sodium diet [29]
- Low glycaemic index/load diet [30]

Either energy restricted diets, iso-caloric, or ad libitum diets will be considered.

The following types of RCTs will be excluded:

- Intervention studies solely based on dietary supplements (e.g. vitamin C, vitamin E, calcium, potassium, garlic, soy protein) or single foods (e.g. nuts);
- Placebo used in any form of dietary supplements (e.g. potassium);
- Studies with an exercise/medication [31] co-intervention that was not applied in all the intervention/control groups;
- Interventions based on very low energy diets (i.e. <600 kcal/day)

Figure 1 shows the network of possible pairwise comparisons between the eligible dietary interventions.

Outcome measures

As mentioned above blood pressure is the most important risk factor for cardiovascular disease. Epidemiological studies show reduction of approximately 3 mmHg in systolic blood pressure has been estimated to reduce risks of CHD by 5–9%, stroke by 8–14%, and all-cause mortality by 4% [32]. Lowering diastolic blood pressure by 5 mmHg reduces the risk of stroke by 32%, and ischemic heart disease by an estimated 20% [33].

Several other systematic reviews and pairwise meta-analysis have included systolic and diastolic blood pressure as outcomes [8, 10].

When blood pressure is measured, the patients should sit for 3-5 minutes before beginning measurement [18].

Search strategy

The search will be performed by LS and CS, and differences resolved by discussion with a third reviewer (HB). We will conduct searches in PubMed, Cochrane CENTRAL, and google scholar. We will search for articles of original research by using the following search terms November 2016:

#1 diet [MeSH Terms]

#2 low-carbohydrate OR high-carbohydrate OR low-fat OR high-fat OR low-protein OR high-protein OR vegetarian OR vegan OR Mediterranean OR DASH OR dietary approaches to stop hypertension OR glycaemic index OR glycaemic load OR Palaeolithic OR low-calorie OR atkins

#3 blood pressure OR hypertension OR diastolic OR systolic

#4 randomized controlled trial OR randomized OR clinical trials as topic OR placebo OR randomly OR trial NOT animals

#5 (#1 AND #2 AND #3 AND #4)

Moreover, the reference lists from the retrieved articles; systematic reviews and meta-analyses will be checked to search for further relevant studies (umbrella review of systematic reviews and meta-analyses). There will be no restrictions on language or publication year. Studies published in languages other than English will be translated by international scientists in our institute.

Study selection process

Two reviewers will independently screen titles and abstracts of all the retrieved bibliographic records. Full texts of all potentially eligible records passing the title and abstract screening level will be retrieved and examined independently by two reviewers (for each database) with the above mentioned eligibility criteria/exclusion criteria [34, 35]. Disagreements will be resolved by consensus or adjudication of another author. A flow-diagram will outline the study selection process and reasons for exclusions (full-text). When a study was published in duplicate, we will include the version containing the most comprehensive information (e.g. longest follow-up duration and/or largest number of study participants).

Data extraction

First author's last name, publication year, country of origin, study design (randomized

controlled trial or cross-over trial), study length, number of arms, participants' sex and age (effect modifier), sample size, diagnostic criteria for hypertension, mean baseline systolic and diastolic blood pressure, mean baseline BMI, method of blood pressure ascertainment, body weight (effect modifier), medication intake (predominately antihypertensive drugs), dietary protocols, dietary assessment method, any physical activity details, participant health status (diabetes mellitus type 2, coronary artery disease), specification of the control group (if available), and where reported: drop-outs, and funding source.

Risk of bias assessment

Full copies of the studies will be independently assessed by two authors for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration [36]. The following sources of bias will be detected: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Randomized controlled trials in nutrition research are often prone to inherent methodological constraints. E.g., they sometimes cannot be controlled with "true" placebos, but rather by a limitation of certain aspects of nutrient compositions, food groups or dietary patterns.

Studies will be classified as being at high risk of bias if achieving fewer than four out of a maximum yield of five low risk of bias items using the risk of bias assessment tool from the Cochrane Collaboration.

Dealing with missing data

We will try to obtain relevant missing data from authors of the included RCTs (by e-mail). If the post-intervention values with the corresponding standard deviations are not available, the change scores with the corresponding standard deviations will be imputed, according the guidelines of the Cochrane Handbook [37].

Evaluation of synthesis assumptions

Data synthesis

Description of the available data

Descriptive statistics for study and population characteristics describing the available data and some important variables (e.g. age, study length, outcome relevant baseline risk factors, etc.) for each pairwise comparison will be generated. We will present the available direct comparisons between different dietary interventions and control groups using a network diagram for each outcome [38]. The size of the nodes will be proportional to the sample size to each dietary intervention and the thickness of the lines proportional to number of studies available. We will also use the contribution matrix to identify the direct comparisons with greater influence in the network relative effects [38, 39].

Standard pairwise meta-analyses and network meta-analyses

For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values or the changes from baseline scores of the different dietary interventions. Separate pairwise meta-analyses will be used first to compare all the interventions with available direct evidence. Heterogeneity between trial results will be measured using the I^2-statistic; I^2 >50% will be considered to represent substantial heterogeneity. Forest plots will be generated to illustrate the study-specific effect sizes along with a 95% CI. Network meta-analysis will be then used to synthesize all the available evidence. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomization of individual trials. We will perform a random effects network meta-analysis for each outcome to estimate all possible pairwise relative effects and obtain a clinically meaningful relative ranking of the different dietary

interventions. We will present summary mean differences in a league table. We will also estimate the relative ranking of the different diets for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA) [40]. For each outcome we will assume a common network-specific heterogeneity parameter and we will estimate the predictive intervals to assess how much this heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies [41].

Assumption of transitivity

Transitivity is the fundamental assumption of indirect comparisons and network meta-analysis, and its violation threatens the validity of the findings obtained from a network of studies. We are considering the following effect modifiers (medication and exercise has been already defined as exclusion criteria if not applied in intervention diets and control groups): changes in body weight and mean baseline age.

Assessment of inconsistency

To evaluate the presence of statistical inconsistency (i.e. disagreement between the different sources of evidence) in the data we will employ both local and global approaches [42]. Specifically, we will use the loop-specific approach [43] to detect loops of evidence that might present important inconsistency as well as the node-splitting approach [44] to detect comparisons for which direct estimates disagree with indirect evidence from the entire network. Global methods investigate the presence of inconsistency jointly from all possible sources in the network. For this purpose we will use the design-by-treatment interaction model and the I^2 statistic [45, 46].

Subgroup and sensitivity analyses

In case of possible important heterogeneity or inconsistency, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses are planned for:

hypertensive status, study length, sample size, age and sex. Sensitivity analyses are planned for diastolic and systolic blood pressure by analysing only studies considered being at low risk of bias.

Small study effects and publication bias

We will use the comparison-adjusted funnel plot [38] to assess the presence of small-study effects in the network and contour-enhanced funnel plots [47] to investigate whether funnel plot asymmetry is likely to be explained by publication bias.

We will fit all analyses described in a frequentist framework using Stata [48] (*network* package [49]) and we will produce presentation tools with the *network graphs* package [50].

Quality of the evidence

We will first use our recently developed NutriGrade-tool to evaluate and judge the meta-evidence for pairwise comparisons, which has been especially developed for nutrition research to address specific requirements for this research field [51]. Then, to infer about the quality of evidence from the network meta-analysis, we will combine our judgement about the direct comparisons with their contributions in the estimation within the network as described by Salanti et al. [42].

Discussion

According to the Global Burden of Disease Group in 2012, unhealthy diet is the leading risk factor for premature death and disability [52]. Given the high prevalence and incidence of hypertension and the potential impact of diet, the conduct of the present systematic review with network meta-analysis is of high clinical and practical relevance. This network meta-analysis will be one of the first to compare the direct and indirect effects of different dietary approaches in the management of hypertension and pre-hypertension. The results of the present network meta-analyses will influence evidence-based treatment decision-making,

since it will be fundamental for reliable recommendations in the management of hypertension and pre-hypertension.

Declarations

Additional file 1: PRISMA-P checklist

Abbreviations: Not applicable

Competing interests: The authors declare that they have no competing interests.

Consent for publication: Not applicable

Ethics approval and consent to participate: Not applicable

Availability of supporting data: Not applicable

Funding: No funding to declare

Acknowledgements: Not applicable

Authors' information: Not applicable

Authors' contributions: LS, AC, HB, GH contributed to the conception and design of the systematic review and meta-analysis. LS, AC, HB, will be involved in the acquisition and analysis of the data. LS, AC, CS, HB, will interpret the results. LS, AC, GH, CS, HB, drafted this protocol. All authors provided critical revisions of the protocol and approved submission of the final manuscript.

References

1. Whelton PK: **Epidemiology of hypertension**. *Lancet* 1994, **344**(8915):101-106.
2. **World Health Organization (2012): Raised Blood Pressure: Situation and Trends. Global Health Observatory http://www.who.int/gho/ncd/risk factors/blood pressure prevalence/en/ (accessed 04.02.2016)**.
3. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW *et al*: **AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation**. *Circulation* 2011, **124**(22):2458-2473.
4. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE *et al*: **2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**. *Circulation* 2014, **129**(25 Suppl 2):S76-99.
5. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM: **Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association**. *Hypertension* 2006, **47**(2):296-308.
6. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH: **Implications of small reductions in diastolic blood pressure for primary prevention**. *Arch Intern Med* 1995, **155**(7):701-709.
7. Staessen JA, Li Y, Thijs L, Wang JG: **Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials**. *Hypertens Res* 2005, **28**(5):385-407.
8. Cornelissen VA, Smart NA: **Exercise training for blood pressure: a systematic review and meta-analysis**. *J Am Heart Assoc* 2013, **2**(1):e004473.
9. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L: **Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(12):1253-1261.
10. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ: **Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. *Adv Nutr* 2016, **7**(1):76-89.
11. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ: **Effect of lower sodium intake on health: systematic review and meta-analyses**. *BMJ* 2013, **346**:f1326.
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement**. *Systematic reviews* 2015, **4**(1):1.
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati AD, Petticrew M, Shekelle P, Stewart LA, the P-PG: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation**. *BMJ* 2015, **349**:g7647.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP *et al*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of**

health care interventions: checklist and explanations. *Ann Intern Med* 2015, **162**(11):777-784.

15. Chaimani A, ., Salanti G, . : **Available from: http://cmimg.cochrane.org/sites/cmimg.cochrane.org/files/uploads/Protocol%20for%20Cochrane%20Reviews%20with%20Multiple%20Interventions.pdf (accessed: 20.01.2016)**.
16. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E: **Dietary advice for reducing cardiovascular risk**. *Cochrane Database Syst Rev* 2013, **12**:CD002128.
17. Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, Stranges S: **'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease**. *Cochrane Database Syst Rev* 2013, **8**:CD009825.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A *et al*: **2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**. *Eur Heart J* 2013, **34**(28):2159-2219.
19. Group TSR: **A Randomized Trial of Intensive versus Standard Blood-Pressure Control**. *New England Journal of Medicine* 2015, **373**(22):2103-2116.
20. Huang PL: **A comprehensive definition for metabolic syndrome**. *Disease Models & Mechanisms* 2009, **2**(5-6):231-237.
21. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM *et al*: **A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group**. *N Engl J Med* 1997, **336**(16):1117-1124.
22. Forman JP, Stampfer MJ, Curhan GC: **Diet and lifestyle risk factors associated with incident hypertension in women**. *JAMA : the journal of the American Medical Association* 2009, **302**(4):401-411.
23. Schwingshackl L, Hoffmann G: **Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(9):929-939.
24. Schwingshackl L, Hoffmann G: **Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis**. *J Acad Nutr Diet* 2013, **113**(12):1640-1661.
25. Schwingshackl L, Hoffmann G: **Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis**. *Nutr J* 2013, **12**:48.
26. Schwingshackl L, Hoffmann G: **Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis**. *Br J Nutr* 2014, **111**(12):2047-2058.
27. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y: **Vegetarian diets and blood pressure: a meta-analysis**. *JAMA Intern Med* 2014, **174**(4):577-587.
28. Jonsson T, Granfeldt Y, Ahren B, Branell UC, Palsson G, Hansson A, Soderstrom M, Lindeberg S: **Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study**. *Cardiovascular diabetology* 2009, **8**:35.

29. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG *et al*: **Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group**. *N Engl J Med* 2001, **344**(1):3-10.
30. Schwingshackl L, Hoffmann G: **Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis**. *Nutr Metab Cardiovasc Dis* 2013, **23**(8):699-706.
31. Schwingshackl L, Missbach B, Dias S, Konig J, Hoffmann G: **Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis**. *Diabetologia* 2014, **57**(9):1789-1797.
32. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC *et al*: **Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program**. *JAMA* 2002, **288**(15):1882-1888.
33. Law M, Wald N, Morris J: **Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy**. *Health Technol Assess* 2003, **7**(31):1-94.
34. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration**. *BMJ* 2009, **339**:b2700.
35. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine* 2009, **6**(7):e1000097.
36. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *BMJ* 2011, **343**:d5928.
37. **Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.** .
38. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G: **Graphical tools for network meta-analysis in STATA**. *PLoS One* 2013, **8**(10):e76654.
39. Krahn U, Binder H, Konig J: **A graphical tool for locating inconsistency in network meta-analyses**. *BMC Med Res Methodol* 2013, **13**:35.
40. Salanti G, Ades AE, Ioannidis JP: **Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial**. *J Clin Epidemiol* 2011, **64**(2):163-171.
41. Riley RD, Higgins JP, Deeks JJ: **Interpretation of random effects meta-analyses**. *BMJ* 2011, **342**:d549.
42. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP: **Evaluating the quality of evidence from a network meta-analysis**. *PLoS One* 2014, **9**(7):e99682.
43. Bucher HC, Guyatt GH, Griffith LE, Walter SD: **The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials**. *J Clin Epidemiol* 1997, **50**(6):683-691.
44. Dias S, Welton NJ, Caldwell DM, Ades AE: **Checking consistency in mixed treatment comparison meta-analysis**. *Stat Med* 2010, **29**(7-8):932-944.

45. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR: **Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies**. *Res Synth Methods* 2012, **3**(2):98-110.
46. Jackson D, Barrett JK, Rice S, White IR, Higgins JP: **A design-by-treatment interaction model for network meta-analysis with random inconsistency effects**. *Stat Med* 2014, **33**(21):3639-3654.
47. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L: **Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry**. *J Clin Epidemiol* 2008, **61**(10):991-996.
48. **StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP**.
49. **White IR. Network meta-analysis. Stata Journal 2015**.
50. **Chaimani, Salanti. Visualizing assumptions and results in network meta-analysis: the network graphs package. Stata Journal 2015.**
51. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopanteils E, Iqbal K *et al*: **NutriGrade: A scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research**. *Adv Nutr* 2016 (accepted 27.06.2016).
52. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M *et al*: **A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**(9859):2224-2260.

Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

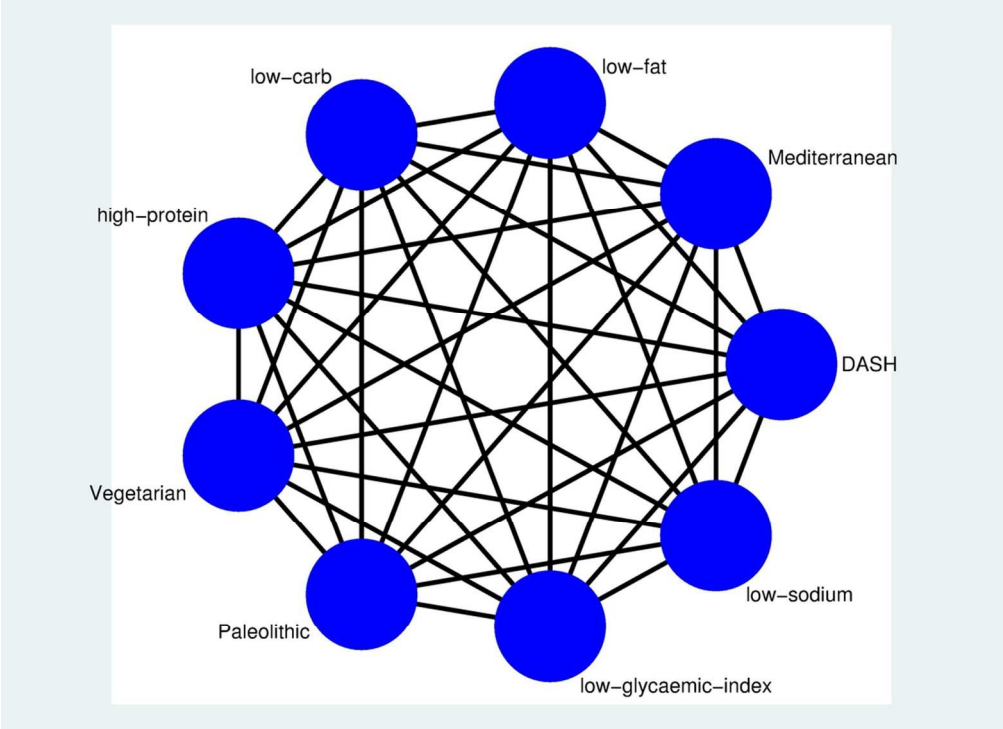

Figure 1: Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

101x73mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐x	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐x	☐	47
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐x	☐	7-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐x	☐	299-303
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐x	☐	296
Sponsor	5b	Provide name for the review funder and/or sponsor	☐x	☐	296
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐x	☐	292

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐x	☐	60-78
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐x	☐	79-88
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐x	☐	96-148
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐x	☐	160-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐x	☐	160-178
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐x	☐	179-188
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐x	☐	179-188
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐x	☐	188-196
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐x	☐	188-196
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐x	☐	150-159
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐x	☐	197-208
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐x	☐	216-244

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐x	☐	216-244
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐x	☐	260-266
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐x	☐	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐x	☐	266-270
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐x	☐	272-278

BMJ Open

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014736.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Dec-2016
Complete List of Authors:	Schwingshackl, Lukas Chaimani, Anna; Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina Hoffmann, Georg; Department of Nutritional Sciences, University of Vienna Schwedhelm, Carolina; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE) Boeing, Heiner; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE)
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, NUTRITION & DIETETICS, PREVENTIVE MEDICINE

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Lukas Schwingshackl[1], Anna Chaimani[2], Georg Hoffmann[3], Carolina Schwedhelm[1], Heiner Boeing[1]

[1] German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

[2] Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina, 45110 Ioannina, Greece

[3] Department of Nutritional Sciences, University of Vienna, Althanstraße 14, 1090 Vienna, Austria

Corresponding author: Lukas Schwingshackl, PhD
Arthur-Scheunert-Allee 114-116; 14558 Nuthetal, Germany
T: +49 (0)33200 88-2712
lukas.schwingshackl@dife.de

Email: anna.chaimani@gmail.com
georg.hoffmann@univie.ac.at
carolina.schwedhelm@dife.de
boeing@dife.de

Abstract

Introduction: Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association, all patients with hypertension should adopt the following dietary advices: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction. The aim of the present study is to assess the efficacy of different dietary approaches on systolic and diastolic blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and Analysis: We will conduct searches in Cochrane Central Register of Controlled Trials in the Cochrane Library, PubMed, and Google Scholar until November 2016. Citations, abstracts, and relevant papers will be screened for eligibility by two reviewers independently. Randomized trials will be included if they meet the following criteria: (1) hypertension (as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) or high normal blood pressure (mean systolic blood pressure: ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), (2) years of age: ≥18, (3) Intervention diets (different type of dietary approaches: e.g. Dietary Approach to Stop Hypertension diet; Mediterranean diet, Vegetarian diet, Paleolithic diet, low sodium diet) either hypo, iso-caloric or ad libitum diets, (4) intervention period ≥12 weeks. For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values (or change scores). Subgroup analyses are planned for: hypertensive status, study length, sample size, age, sex.

Ethics and Dissemination: As this study is based solely on the published literature, no ethics approval is required. We will publish our network meta-analysis in a peer-reviewed scientific journal.

Systematic Review Registration: PROSPERO: CRD42016049243

Keywords: diet, hypertension, blood pressure, network meta-analysis, evidence synthesis, systematic review

Strengths and limitations of this study

- The protocol addresses the important question of which dietary approach offers the most benefits in the management of elevated blood pressure
- The present network meta-analysis has a clearly established aim and, stringent inclusion criteria, state of the art methods for data collection and quantitative and qualitative synthesis
- Limitations include variations in trial designs and regimen, adherence to dietary protocols, lack of blinding across the included intervention trials and ecological fallacy

Background

Due to its frequent occurrence and high impact on the development of cardiovascular and kidney disease, hypertension is one of the most challenging problems adversely affecting public-health worldwide [1]. The prevalence of hypertension accounts for nearly 40% of people older than 25 years worldwide, and the number or patients has increased from 600 million to a billion in 2008 [2].

Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association and the European Society of Cardiology and Hypertension all patients with hypertension, should follow dietary modifications: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction [3, 4].

Accumulating evidence indicates that dietary factors have a predominant role in the management of elevated blood pressure [5]. In individuals without hypertension, dietary changes reduce blood pressure and prevent hypertension, thereby lowering the risk of blood pressure related complications. Epidemiological studies suggest that even slight reductions in blood pressure will reduce the risk of cardiovascular disease [6, 7].

Whereas its already well established that aerobic exercise is more effective in reducing blood pressure in hypertensive patients compared to resistance training [8], the question regarding the most effective dietary approach in the treatment of hypertension and high normal pressure has not been evaluated.

To our knowledge, no up to date systematic review and network meta-analysis has been conducted to compare different dietary modifications in the management of hypertension and high normal blood pressure. Some pairwise meta-analyses have been published comparing DASH dietary approaches [9], combined dietary approaches [10], and lower sodium intake vs usual care/control diet [11]. One of the most important questions that remain to be answered

is which dietary approach offers the most benefits in the management of elevated blood pressure.

Therefore, our aim is to compare the efficacy of different dietary approaches on blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and design

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016049243). The present systematic review protocol was planned, conducted, and reported in adherence to standards of quality for reporting systematic reviews and network meta-analysis protocols [12-15] (additional file 1).

Eligibility criteria

Studies will be included in the meta-analysis if they meet all of the following criteria:

Types of studies

Randomized trial design comparison between different dietary approaches (e.g. Dietary Approach to Stop Hypertension; Mediterranean diet; Vegetarian diet; Palaeolithic diet; low sodium diet; low fat diet; low carbohydrate diet; high protein diet; low glycaemic index/load diet) with a minimum intervention period of 3 months according to recent Cochrane Reviews on diet and cardiovascular risk [16, 17].

Types of participants

We will consider only adults with a mean age ≥18 years. Hypertension was defined according to the European Society of Cardiology and European Society of Cardiology & Hypertension as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure. Moreover, all patients taking antihypertensive medication will be included [18].

High normal blood pressure (mean systolic blood pressure ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), was also defined according to the European Society of Cardiology & Hypertension and the recently published SPRINT trial [18, 19]. Including patients with “high normal” blood pressure is of major relevance since it is part of the metabolic syndrome diagnosis criteria [20].

Types of Interventions

Accumulating evidence indicates that dietary factors play an important role in the treatment of elevated blood pressure. Likewise, dietary modifications decrease blood pressure [21] and reduce the risk of hypertension in people without established high blood pressure [22]. Even if modest, a reduction in blood pressure can have an important impact on the health of entire populations [5]. We will include all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets.

Eligible types of dietary approaches will be as follows:

- Dietary Approach to Stop Hypertension (DASH): high intake of fruits & vegetables, low-fat dairy, whole grain [21]
- Mediterranean dietary pattern: olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals [23]
- Low carbohydrate diet (<30% carbohydrates of total energy intake, high intakes of animal high in animal or/and plant protein) [24]
- High protein diet [25] (≥ 25% protein of total energy intake)
- Low fat diet (<30% fat of total energy intake, high in grains and cereals) [24, 26]
- Vegetarian diet (no meat or fish) [27]
- Palaeolithic diet (lean meat, fish, eggs, vegetables, fruits, berries, and nuts; Dairy products, cereals, added salt, and refined fats and sugar were excluded) [28]
- Low sodium diet [29]
- Low glycaemic index/load diet [30]

Either energy restricted diets, iso-caloric, or ad libitum diets will be considered.

The following types of RCTs will be excluded:

- Intervention studies solely based on dietary supplements (e.g. vitamin C, vitamin E, calcium, potassium, garlic, soy protein) or single foods (e.g. nuts);
- Placebo used in any form of dietary supplements (e.g. potassium);
- Studies with an exercise/medication [31] co-intervention that was not applied in all the intervention/control groups;
- Interventions based on very low energy diets (i.e. <600 kcal/day)

Figure 1 shows the network of possible pairwise comparisons between the eligible dietary interventions. If we identify a study, which combines low sodium and a low fat diet (and not fulfil the criteria of a DASH diet), we will handle this study as evaluating a different dietary regimen (low fat + low sodium) in the network meta-analysis. If food-based interventions fulfil also the criteria of a nutrient-based dietary regimen, we will perform sensitivity analysis for food-based vs. nutrient based dietary regimen taking into account possible overlaps.

Outcome measures

Although cardiovascular diseases are determined by variables which cannot be influenced such as age or heritability [32, 33], there are several predictors for CVD that can be affected by lifestyle improvements. As mentioned above, blood pressure is the most important of these modifiable risk factors. Epidemiological studies show that a reduction of approximately 3 mmHg in systolic blood pressure has been estimated to reduce risks of CHD by 5–9%, stroke by 8–14%, and all-cause mortality by 4% [34]. Lowering diastolic blood pressure by 5 mmHg reduces the risk of stroke by 32%, and ischemic heart disease by an estimated 20% [35].

Several other systematic reviews and pairwise meta-analysis have included systolic and diastolic blood pressure as outcomes [9, 10]. In order to achieve a better comparability between the data compiled by different studies, the patients should ideally hold a sitting position for 3-5 minutes prior to blood pressure measurement [18].

Search strategy

The search will be performed by LS and CS, and differences resolved by discussion with a third reviewer (HB). We will conduct searches in PubMed, Cochrane CENTRAL, and google scholar. We will search for articles of original research by using the following search terms:

#1 diet [MeSH Terms]

#2 low carbohydrate OR high carbohydrate OR low fat OR high fat OR low protein OR high protein OR vegetarian OR vegan OR Mediterranean OR DASH OR dietary approaches to stop hypertension OR low glycaemic index OR low glycaemic load OR Palaeolithic OR low-calorie OR atkins OR low sodium

#3 blood pressure OR hypertension OR diastolic OR systolic

#4 random* NOT animals

#5 (#1 AND #2 AND #3 AND #4)

Moreover, the reference lists from the retrieved articles, systematic reviews and meta-analyses will be checked to search for further relevant studies (umbrella review of systematic reviews and meta-analyses). There will be no restrictions on language or publication year. Studies published in languages other than English will be translated by international scientists in our institute.

Study selection process

Two reviewers will independently screen titles and abstracts of all the retrieved bibliographic records. Full texts of all potentially eligible records passing the title and abstract screening level will be retrieved and examined independently by two reviewers (for each database) with the above mentioned eligibility criteria/exclusion criteria [36, 37]. Disagreements will be resolved by consensus or adjudication of another author. A flow-diagram will outline the study selection process and reasons for exclusions. If a study is published in duplicate, we will include the version containing the most comprehensive information (e.g. longest follow-up duration and/or largest number of study participants).

Data extraction

The following data will be extracted from each study: first author's last name, publication year, country of origin, study design (randomized trial or cross-over trial), study length, number of arms, participants' sex and age (effect modifier), sample size, diagnostic criteria for hypertension, mean baseline systolic and diastolic blood pressure, mean baseline BMI, method of blood pressure ascertainment, body weight (effect modifier), medication intake (predominately antihypertensive drugs), dietary protocols, dietary assessment method, any physical activity details, participant health status (diabetes mellitus type 2, coronary artery disease, alcohol intake, smoking), specification of the control group (if available), and where reported: drop-outs, and funding source.

Risk of bias assessment

Full copies of the studies will be independently assessed by two authors for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration [38]. The following sources of bias will be assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Randomized controlled trials in nutrition research are often prone to inherent methodological constraints. For example they sometimes cannot be controlled with "true" placebos, but rather by a limitation of certain aspects of nutrient compositions, food groups or dietary patterns.

Studies will be classified as being at high risk of bias if achieving fewer than four out of a maximum yield of five low risk of bias items using the risk of bias assessment tool from the Cochrane Collaboration.

Dealing with missing data

We will try to obtain relevant missing data from authors of the included randomized trials (by

e-mail). If the post-intervention values with the corresponding standard deviations are not available, the change scores with the corresponding standard deviations will be imputed, according to the guidelines of the Cochrane Handbook [39].

Evaluation of synthesis assumptions

Data synthesis

Description of the available data

Descriptive statistics for study and population characteristics describing the available data and selected variables (e.g. age, study length, outcome relevant baseline risk factors, etc.) for each pairwise comparison will be generated. We will present the available direct comparisons between different dietary interventions and control groups using a network diagram for each outcome [40]. The size of the nodes (circles) will be proportional to the sample size to each dietary intervention and the thickness of the edges (lines) proportional to number of studies available. We will also use the contribution matrix to identify the direct comparisons with greater influence on the network relative effects [40, 41].

Standard pairwise meta-analyses and network meta-analyses

For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values or the changes from baseline scores of the different dietary interventions. Intention-to-treat analysis data will be used when it is available. Separate pairwise meta-analyses will be used first to compare all the interventions with available direct evidence. Heterogeneity between trial results will be measured using the I^2-statistic; I^2 >50% will be considered to represent substantial heterogeneity. Forest plots will be generated to illustrate the study-specific effect sizes along with a 95% CI. Network meta-analysis will be then used to synthesize all the available

evidence. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomization of individual trials. We will perform a random effects network meta-analysis for each outcome to estimate all possible pairwise relative effects and obtain a clinically meaningful relative ranking of the different dietary interventions. Multi-arm trials will be modeled properly accounting for the correlation in the effect sizes from such studies. We will present summary mean differences in a league table. We will also estimate the relative ranking of the different diets for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA) [42]. For each outcome we will assume a common network-specific heterogeneity parameter and we will estimate the predictive intervals to assess how much this heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies [43].

Assumption of transitivity

Transitivity is the fundamental assumption of indirect comparisons and network meta-analysis, and its violation threatens the validity of the findings obtained from a network of studies. We plan on including changes in body weight and mean baseline age as potential effect modifiers.

Assessment of inconsistency

To evaluate the presence of statistical inconsistency (i.e. disagreement between the different sources of evidence) in the data we will employ both local and global approaches [44]. Specifically, we will use the loop-specific approach [45] to detect loops of evidence that might present important inconsistency as well as the node-splitting approach [46] to detect comparisons for which direct estimates disagree with indirect evidence from the entire network. Global methods investigate the presence of inconsistency jointly from all possible sources in the network. For this purpose, we will use the design-by-treatment interaction

model and the I^2 statistic [47, 48].

Subgroup and sensitivity analyses

In case of possible important heterogeneity or inconsistency, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses are planned for hypertensive status, comorbidities, study length (shorter vs. longer-term), sample size, age and sex. Sensitivity analyses are planned for diastolic and systolic blood pressure by analysing only studies considered being at low risk of bias.

Small study effects and publication bias

We will use the comparison-adjusted funnel plot [40] to assess the presence of small-study effects in the network and contour-enhanced funnel plots [49] to investigate whether funnel plot asymmetry is likely to be explained by publication bias.

We will fit all analyses described in a frequentist framework using Stata [50] (*network* package [51]) and we will produce presentation tools with the *network graphs* package [52].

In case that publication bias will be detected we will attempt to fit a selection model that models the relationship between relative effects and probability of a study for being published and we will obtain relative effects 'adjusted' for the impact of publication bias [53].

Quality of the evidence

We will first use our recently developed NutriGrade-tool to evaluate and judge the meta-evidence for pairwise comparisons, which has been especially developed for nutrition research to address specific requirements for this research field [54]. Then, to infer about the quality of evidence from the network meta-analysis, we will combine our judgement about the direct comparisons with their contributions in the estimation within the network as described by Salanti et al. [44].

Discussion

According to the Global Burden of Disease Group in 2012, unhealthy diet is the leading risk factor for premature death and disability [55]. Given the high prevalence and incidence of hypertension and the potential impact of diet, the conduct of the present systematic review with network meta-analysis is of high clinical and practical relevance. This network meta-analysis will be one of the first to compare the direct and indirect effects of different dietary approaches in the management of hypertension and pre-hypertension. The results of the present network meta-analyses will influence evidence-based treatment decision-making, since it will be fundamental for reliable recommendations in the management of hypertension and pre-hypertension.

Declarations

Additional file 1: PRISMA-P checklist

Abbreviations: Not applicable

Competing interests: The authors declare that they have no competing interests.

Consent for publication: Not applicable

Ethics approval and consent to participate: Not applicable

Availability of supporting data: Not applicable

Funding: No funding to declare

Acknowledgements: Not applicable

Authors' information: Not applicable

Authors' contributions: LS, AC, HB, GH contributed to the conception and design of the systematic review and meta-analysis. LS, AC, HB, will be involved in the acquisition and analysis of the data. LS, AC, CS, HB, will interpret the results. LS, AC, GH, CS, HB, drafted this protocol. All authors provided critical revisions of the protocol and approved submission of the final manuscript.

314

References

1. Whelton PK: **Epidemiology of hypertension**. *Lancet* 1994, **344**(8915):101-106.
2. Wikstrom K, Lindstrom J, Harald K, Peltonen M, Laatikainen T: **Clinical and lifestyle-related risk factors for incident multimorbidity: 10-year follow-up of Finnish population-based cohorts 1982-2012**. *European Journal of Internal Medicine* 2015, **26**(3):211-216.
3. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW *et al*: **AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation**. *Circulation* 2011, **124**(22):2458-2473.
4. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE *et al*: **2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**. *Circulation* 2014, **129**(25 Suppl 2):S76-99.
5. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM: **Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association**. *Hypertension* 2006, **47**(2):296-308.
6. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH: **Implications of small reductions in diastolic blood pressure for primary prevention**. *Arch Intern Med* 1995, **155**(7):701-709.
7. Staessen JA, Li Y, Thijs L, Wang JG: **Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials**. *Hypertens Res* 2005, **28**(5):385-407.
8. Cornelissen VA, Smart NA: **Exercise training for blood pressure: a systematic review and meta-analysis**. *J Am Heart Assoc* 2013, **2**(1):e004473.
9. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L: **Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(12):1253-1261.
10. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ: **Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. *Adv Nutr* 2016, **7**(1):76-89.
11. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ: **Effect of lower sodium intake on health: systematic review and meta-analyses**. *BMJ* 2013, **346**:f1326.
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement**. *Systematic reviews* 2015, **4**(1):1.
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati AD, Petticrew M, Shekelle P, Stewart LA, the P-PG: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation**. *BMJ* 2015, **349**:g7647.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP *et al*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of**

health care interventions: checklist and explanations. *Ann Intern Med* 2015, **162**(11):777-784.

15. Chaimani A, ., Salanti G, . : **Available from: http://cmimg.cochrane.org/sites/cmimg.cochrane.org/files/uploads/Protocol%20for%20Cochrane%20Reviews%20with%20Multiple%20Interventions.pdf (accessed: 20.01.2016)**.
16. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E: **Dietary advice for reducing cardiovascular risk**. *Cochrane Database Syst Rev* 2013, **12**:CD002128.
17. Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, Stranges S: **'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease**. *Cochrane Database Syst Rev* 2013, **8**:CD009825.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A *et al*: **2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**. *Eur Heart J* 2013, **34**(28):2159-2219.
19. Group TSR: **A Randomized Trial of Intensive versus Standard Blood-Pressure Control**. *New England Journal of Medicine* 2015, **373**(22):2103-2116.
20. Huang PL: **A comprehensive definition for metabolic syndrome**. *Disease Models & Mechanisms* 2009, **2**(5-6):231-237.
21. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM *et al*: **A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group**. *N Engl J Med* 1997, **336**(16):1117-1124.
22. Forman JP, Stampfer MJ, Curhan GC: **Diet and lifestyle risk factors associated with incident hypertension in women**. *JAMA : the journal of the American Medical Association* 2009, **302**(4):401-411.
23. Schwingshackl L, Hoffmann G: **Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(9):929-939.
24. Schwingshackl L, Hoffmann G: **Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis**. *J Acad Nutr Diet* 2013, **113**(12):1640-1661.
25. Schwingshackl L, Hoffmann G: **Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis**. *Nutr J* 2013, **12**:48.
26. Schwingshackl L, Hoffmann G: **Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis**. *Br J Nutr* 2014, **111**(12):2047-2058.
27. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y: **Vegetarian diets and blood pressure: a meta-analysis**. *JAMA Intern Med* 2014, **174**(4):577-587.
28. Jonsson T, Granfeldt Y, Ahren B, Branell UC, Palsson G, Hansson A, Soderstrom M, Lindeberg S: **Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study**. *Cardiovascular diabetology* 2009, **8**:35.

29. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG *et al*: **Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group**. *N Engl J Med* 2001, **344**(1):3-10.
30. Schwingshackl L, Hoffmann G: **Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis**. *Nutr Metab Cardiovasc Dis* 2013, **23**(8):699-706.
31. Schwingshackl L, Missbach B, Dias S, Konig J, Hoffmann G: **Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis**. *Diabetologia* 2014, **57**(9):1789-1797.
32. Kessler T, Vilne B, Schunkert H: **The impact of genome-wide association studies on the pathophysiology and therapy of cardiovascular disease**. *EMBO molecular medicine* 2016, **8**(7):688-701.
33. North BJ, Sinclair DA: **The intersection between aging and cardiovascular disease**. *Circulation research* 2012, **110**(8):1097-1108.
34. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC *et al*: **Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program**. *JAMA* 2002, **288**(15):1882-1888.
35. Law M, Wald N, Morris J: **Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy**. *Health Technol Assess* 2003, **7**(31):1-94.
36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration**. *BMJ* 2009, **339**:b2700.
37. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine* 2009, **6**(7):e1000097.
38. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *BMJ* 2011, **343**:d5928.
39. Ticinesi A, Nouvenne A, Lauretani F, Prati B, Cerundolo N, Maggio M, Meschi T: **Survival in older adults with dementia and eating problems: To PEG or not to PEG?** *Clinical Nutrition* 2016, **35**(6):1512-1516.
40. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G: **Graphical tools for network meta-analysis in STATA**. *PLoS One* 2013, **8**(10):e76654.
41. Krahn U, Binder H, Konig J: **A graphical tool for locating inconsistency in network meta-analyses**. *BMC Med Res Methodol* 2013, **13**:35.
42. Salanti G, Ades AE, Ioannidis JP: **Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial**. *J Clin Epidemiol* 2011, **64**(2):163-171.
43. Riley RD, Higgins JP, Deeks JJ: **Interpretation of random effects meta-analyses**. *BMJ* 2011, **342**:d549.
44. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP: **Evaluating the quality of evidence from a network meta-analysis**. *PLoS One* 2014, **9**(7):e99682.

45. Bucher HC, Guyatt GH, Griffith LE, Walter SD: **The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials**. *J Clin Epidemiol* 1997, **50**(6):683-691.
46. Dias S, Welton NJ, Caldwell DM, Ades AE: **Checking consistency in mixed treatment comparison meta-analysis**. *Stat Med* 2010, **29**(7-8):932-944.
47. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR: **Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies**. *Res Synth Methods* 2012, **3**(2):98-110.
48. Jackson D, Barrett JK, Rice S, White IR, Higgins JP: **A design-by-treatment interaction model for network meta-analysis with random inconsistency effects**. *Stat Med* 2014, **33**(21):3639-3654.
49. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L: **Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry**. *J Clin Epidemiol* 2008, **61**(10):991-996.
50. Flint A, New K, Davies MW: **Cup feeding versus other forms of supplemental enteral feeding for newborn infants unable to fully breastfeed**. *Cochrane Database of Systematic Reviews* 2016, **2016 (8) (no pagination)**(CD005092).
51. Verreth A, Peeters A, Van Regenmortel N, De Laet I, Schoonheydt K, Dits H, Van De Vyvere M, Libeer C, Meersseman W, Malbrain MLNG: **Prognostic value of serum galactomannan in mixed ICU patients: A retrospective observational study**. *Anaesthesiology Intensive Therapy* 2014, **46**(3):145-154.
52. Ambartsumyan L, Flores A, Nurko S, Rodriguez L: **Utility of Octreotide in Advancing Enteral Feeds in Children with Chronic Intestinal Pseudo-Obstruction**. *Pediatric Drugs* 2016, **18**(5):387-392.
53. Mavridis D, Welton NJ, Sutton A, Salanti G: **A selection model for accounting for publication bias in a full network meta-analysis**. *Statistics in medicine* 2014, **33**(30):5399-5412.
54. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopanteils E, Iqbal K *et al*: **Perspective: NutriGrade: A Scoring System to Assess and Judge the Meta-Evidence of Randomized Controlled Trials and Cohort Studies in Nutrition Research**. *Advances in Nutrition: An International Review Journal* 2016, **7**(6):994-1004.
55. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M *et al*: **A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**(9859):2224-2260.

Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

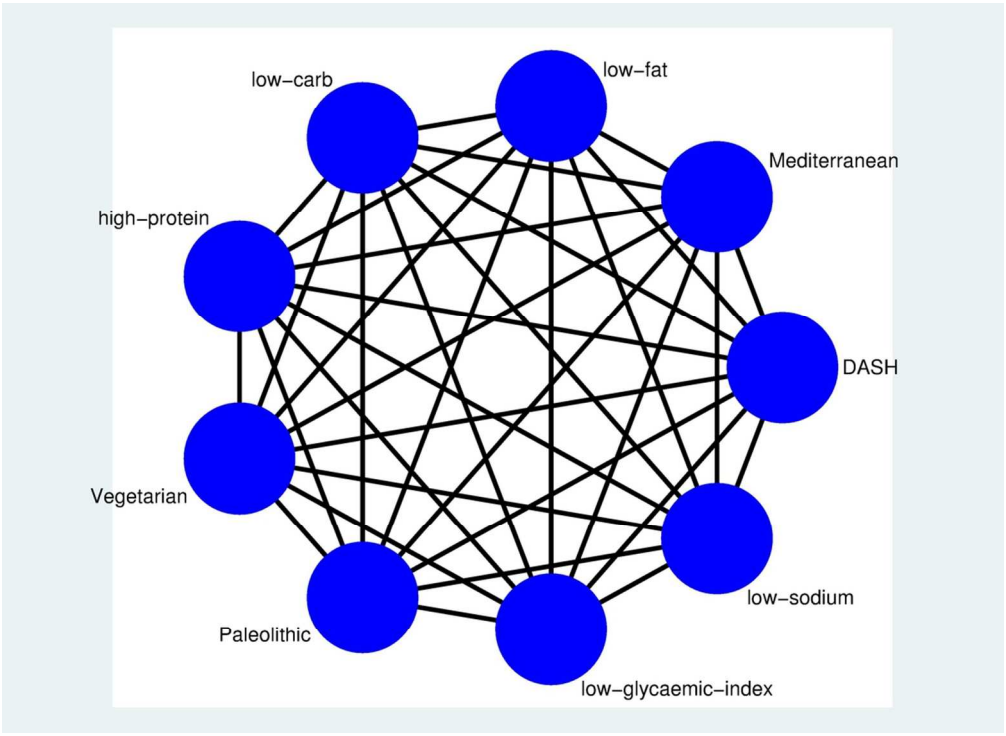

Figure 1: Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

101x73mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐x	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐x	☐	47
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐x	☐	7-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐x	☐	299-303
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐x	☐	296
Sponsor	5b	Provide name for the review funder and/or sponsor	☐x	☐	296
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐x	☐	292

2

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐x	☐	60-78
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐x	☐	79-88
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐x	☐	96-148
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐x	☐	160-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐x	☐	160-178
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐x	☐	179-188
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐x	☐	179-188
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐x	☐	188-196
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐x	☐	188-196
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐x	☐	150-159
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐x	☐	197-208
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐x	☐	216-244

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐x	☐	216-244
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐x	☐	260-266
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐x	☐	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐x	☐	266-270
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐x	☐	272-278

BMJ Open

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014736.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Jan-2017
Complete List of Authors:	Schwingshackl, Lukas Chaimani, Anna; Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina Hoffmann, Georg; Department of Nutritional Sciences, University of Vienna Schwedhelm, Carolina; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE) Boeing, Heiner; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE)
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, NUTRITION & DIETETICS, PREVENTIVE MEDICINE

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Lukas Schwingshackl[1], Anna Chaimani[2], Georg Hoffmann[3], Carolina Schwedhelm[1], Heiner Boeing[1]

[1] German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

[2] Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina, 45110 Ioannina, Greece

[3] Department of Nutritional Sciences, University of Vienna, Althanstraße 14, 1090 Vienna, Austria

Corresponding author: Lukas Schwingshackl, PhD
Arthur-Scheunert-Allee 114-116; 14558 Nuthetal, Germany
T: +49 (0)33200 88-2712
lukas.schwingshackl@dife.de

Email: anna.chaimani@gmail.com
georg.hoffmann@univie.ac.at
carolina.schwedhelm@dife.de
boeing@dife.de

Abstract

Introduction: Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association, all patients with hypertension should adopt the following dietary advices: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction. The aim of the present study is to assess the efficacy of different dietary approaches on systolic and diastolic blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and Analysis: We will conduct searches in Cochrane Central Register of Controlled Trials in the Cochrane Library, PubMed, and Google Scholar until November 2016. Citations, abstracts, and relevant papers will be screened for eligibility by two reviewers independently. Randomized trials will be included if they meet the following criteria: (1) hypertension (as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) or high normal blood pressure (mean systolic blood pressure: ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), (2) years of age: ≥18, (3) Intervention diets (different type of dietary approaches: e.g. Dietary Approach to Stop Hypertension diet; Mediterranean diet, Vegetarian diet, Paleolithic diet, low sodium diet) either hypo, iso-caloric or ad libitum diets, (4) intervention period ≥12 weeks. For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values (or change scores). Subgroup analyses are planned for: hypertensive status, study length, sample size, age, sex.

Ethics and Dissemination: As this study is based solely on the published literature, no ethics approval is required. We will publish our network meta-analysis in a peer-reviewed scientific journal.

Systematic Review Registration: PROSPERO: CRD42016049243

Keywords: diet, hypertension, blood pressure, network meta-analysis, evidence synthesis, systematic review

Strengths and limitations of this study

- The protocol addresses the important question of which dietary approach offers the most benefits in the management of elevated blood pressure
- The present network meta-analysis has a clearly established aim and, stringent inclusion criteria, state of the art methods for data collection and quantitative and qualitative synthesis
- Limitations include variations in trial designs and regimen, adherence to dietary protocols, lack of blinding across the included intervention trials and ecological fallacy

Background

Due to its frequent occurrence and high impact on the development of cardiovascular and kidney disease, hypertension is one of the most challenging problems adversely affecting public-health worldwide [1]. The prevalence of hypertension accounts for nearly 40% of people older than 25 years worldwide, and the number or patients has increased from 600 million to a billion in 2008 [2].

Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association and the European Society of Cardiology and Hypertension all patients with hypertension, should follow dietary modifications: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction [3, 4].

Accumulating evidence indicates that dietary factors have a predominant role in the management of elevated blood pressure [5]. In individuals without hypertension, dietary changes reduce blood pressure and prevent hypertension, thereby lowering the risk of blood pressure related complications. Epidemiological studies suggest that even slight reductions in blood pressure will reduce the risk of cardiovascular disease [6, 7].

Whereas its already well established that aerobic exercise is more effective in reducing blood pressure in hypertensive patients compared to resistance training [8], the question regarding the most effective dietary approach in the treatment of hypertension and high normal pressure has not been evaluated.

To our knowledge, no up to date systematic review and network meta-analysis has been conducted to compare different dietary modifications in the management of hypertension and high normal blood pressure. Some pairwise meta-analyses have been published comparing DASH dietary approaches [9], combined dietary approaches [10], and lower sodium intake vs usual care/control diet [11]. One of the most important questions that remain to be answered

is which dietary approach offers the most benefits in the management of elevated blood pressure.

Therefore, our aim is to compare the efficacy of different dietary approaches on blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and design

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016049243). The present systematic review protocol was planned, conducted, and reported in adherence to standards of quality for reporting systematic reviews and network meta-analysis protocols [12-15] (additional file 1).

Eligibility criteria

Studies will be included in the meta-analysis if they meet all of the following criteria:

Types of studies

Randomized trial design comparison between different dietary approaches (e.g. Dietary Approach to Stop Hypertension; Mediterranean diet; Vegetarian diet; Palaeolithic diet; low sodium diet; low fat diet; low carbohydrate diet; high protein diet; low glycaemic index/load diet) with a minimum intervention period of 3 months according to recent Cochrane Reviews on diet and cardiovascular risk [16, 17]. If randomized trials have more than one different length of outcomes (e.g. 12 weeks and 12 months), we will include the long-term data.

Types of participants

We will consider only adults with a mean age ≥18 years. Hypertension was defined according to the European Society of Cardiology and European Society of Cardiology & Hypertension as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure. Moreover, all patients taking antihypertensive medication will be included [18].

High normal blood pressure (mean systolic blood pressure ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), was also defined according to the European Society of Cardiology & Hypertension and the recently published SPRINT trial [18, 19]. Including patients with “high normal” blood pressure is of major relevance since it is part of the metabolic syndrome diagnosis criteria [20].

Types of Interventions

Accumulating evidence indicates that dietary factors play an important role in the treatment of elevated blood pressure. Likewise, dietary modifications decrease blood pressure [21] and reduce the risk of hypertension in people without established high blood pressure [22]. Even if modest, a reduction in blood pressure can have an important impact on the health of entire populations [5]. We will include all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets (direct evidence).

Eligible types of dietary approaches will be as follows:

- Dietary Approach to Stop Hypertension (DASH): high intake of fruits & vegetables, low-fat dairy, whole grain [21]
- Mediterranean dietary pattern: olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals [23-27]
- Low carbohydrate diet (<30% carbohydrates of total energy intake, high intakes of animal high in animal or/and plant protein) [28]
- High protein diet [29] (≥ 25% protein of total energy intake)
- Low fat diet (<30% fat of total energy intake, high in grains and cereals) [28, 30]
- Vegetarian diet (no meat or fish) [31]
- Palaeolithic diet (lean meat, fish, eggs, vegetables, fruits, berries, and nuts; Dairy products, cereals, added salt, and refined fats and sugar were excluded) [32]
- Low sodium diet [33]
- Low glycaemic index/load diet [34]

Either energy restricted diets, iso-caloric, or ad libitum diets will be considered.

The following types of RCTs will be excluded:

- Intervention studies solely based on dietary supplements (e.g. vitamin C, vitamin E, calcium, potassium, garlic, soy protein) or single foods (e.g. nuts);
- Placebo used in any form of dietary supplements (e.g. potassium);
- Studies with an exercise/medication [35, 36] co-intervention that was not applied in all the intervention/control groups;
- Interventions based on very low energy diets (i.e. <600 kcal/day)

Figure 1 shows the network of possible pairwise comparisons between the eligible dietary interventions. If we identify a study, which combines low sodium and a low fat diet (and not fulfil the criteria of a DASH diet), we will handle this study as evaluating a different dietary regimen (low fat + low sodium) in the network meta-analysis. If food-based interventions fulfil also the criteria of a nutrient-based dietary regimen, we will perform sensitivity analysis for food-based vs. nutrient based dietary regimen taking into account possible overlaps.

Outcome measures

Although cardiovascular diseases are determined by variables which cannot be influenced such as age or heritability [37, 38], there are several predictors for CVD that can be affected by lifestyle improvements. As mentioned above, blood pressure is the most important of these modifiable risk factors. Epidemiological studies show that a reduction of approximately 3 mmHg in systolic blood pressure has been estimated to reduce risks of CHD by 5–9%, stroke by 8–14%, and all-cause mortality by 4% [39]. Lowering diastolic blood pressure by 5 mmHg reduces the risk of stroke by 32%, and ischemic heart disease by an estimated 20% [40].

Several other systematic reviews and pairwise meta-analysis have included systolic and diastolic blood pressure as outcomes [9, 10]. In order to achieve a better comparability between the data compiled by different studies, the patients should ideally hold a sitting position for 3-5 minutes prior to blood pressure measurement [18].

Search strategy

The search will be performed by LS and CS, and differences resolved by discussion with a third reviewer (HB). We will conduct searches in PubMed, Cochrane CENTRAL, and google scholar. We will search for articles of original research by using the following search terms:

#1 diet [MeSH Terms]

#2 low carbohydrate OR high carbohydrate OR low fat OR high fat OR low protein OR high protein OR vegetarian OR vegan OR Mediterranean OR DASH OR dietary approaches to stop hypertension OR low glycaemic index OR low glycaemic load OR Palaeolithic OR low-calorie OR atkins OR low sodium

#3 blood pressure OR hypertension OR diastolic OR systolic

#4 random* NOT animals

#5 (#1 AND #2 AND #3 AND #4)

Moreover, the reference lists from the retrieved articles, systematic reviews and meta-analyses will be checked to search for further relevant studies (umbrella review of systematic reviews and meta-analyses). There will be no restrictions on language or publication year. Studies published in languages other than English will be translated by international scientists in our institute.

Study selection process

Two reviewers will independently screen titles and abstracts of all the retrieved bibliographic records. Full texts of all potentially eligible records passing the title and abstract screening level will be retrieved and examined independently by two reviewers (for each database) with the above mentioned eligibility criteria/exclusion criteria [41, 42]. Disagreements will be resolved by consensus or adjudication of another author. A flow-diagram will outline the study selection process and reasons for exclusions. If a study is published in duplicate, we will include the version containing the most comprehensive information (e.g. longest follow-up duration and/or largest number of study participants).

Data extraction

The following data will be extracted from each study: first author's last name, publication year, country of origin, study design (randomized trial or cross-over trial), study length, number of arms, participants' sex and age (effect modifier), sample size, diagnostic criteria for hypertension, mean baseline systolic and diastolic blood pressure, mean baseline BMI, method of blood pressure ascertainment, body weight (effect modifier), medication intake (predominately antihypertensive drugs), dietary protocols, dietary assessment method, any physical activity details, participant health status (diabetes mellitus type 2, coronary artery disease, alcohol intake, smoking), specification of the control group (if available), and where reported: drop-outs, and funding source.

Risk of bias assessment

Full copies of the studies will be independently assessed by two authors for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration [43]. The following sources of bias will be assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Randomized controlled trials in nutrition research are often prone to inherent methodological constraints. For example, they sometimes cannot be controlled with "true" placebos, but rather by a limitation of certain aspects of nutrient compositions, food groups or dietary patterns.

Studies will be classified as being at high risk of bias if achieving fewer than four out of a maximum yield of five low risk of bias items using the risk of bias assessment tool from the Cochrane Collaboration.

Dealing with missing data

We will try to obtain relevant missing data from authors of the included randomized trials (by

e-mail). If the post-intervention values with the corresponding standard deviations are not available, the change scores with the corresponding standard deviations will be imputed, according to the guidelines of the Cochrane Handbook [44].

Evaluation of synthesis assumptions

Data synthesis

Description of the available data

Descriptive statistics for study and population characteristics describing the available data and selected variables (e.g. age, study length, outcome relevant baseline risk factors, etc.) for each pairwise comparison will be generated. We will present the available direct comparisons between different dietary interventions and control groups using a network diagram for each outcome [45]. The size of the nodes (circles) will be proportional to the sample size to each dietary intervention and the thickness of the edges (lines) proportional to number of studies available. We will also use the contribution matrix to identify the direct comparisons with greater influence on the network relative effects [45, 46].

Standard pairwise meta-analyses and network meta-analyses

For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values or the changes from baseline scores of the different dietary interventions. Intention-to-treat analysis data will be used when it is available. Separate pairwise meta-analyses will be used first to compare all the interventions with available direct evidence. Heterogeneity between trial results will be measured using the I^2-statistic; I^2 >50% will be considered to represent substantial heterogeneity. Forest plots will be generated to illustrate the study-specific effect sizes along with a 95% CI. Network meta-analysis will be then used to synthesize all the available

evidence. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomization of individual trials. We will perform a random effects network meta-analysis for each outcome to estimate all possible pairwise relative effects and obtain a clinically meaningful relative ranking of the different dietary interventions. Multi-arm trials will be modeled properly accounting for the correlation in the effect sizes from such studies. We will present summary mean differences in a league table. We will also estimate the relative ranking of the different diets for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA) [47]. For each outcome we will assume a common network-specific heterogeneity parameter and we will estimate the predictive intervals to assess how much this heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies [48].

Assumption of transitivity

Transitivity is the fundamental assumption of indirect comparisons and network meta-analysis, and its violation threatens the validity of the findings obtained from a network of studies. We plan on including changes in body weight and mean baseline age as potential effect modifiers.

Assessment of inconsistency

To evaluate the presence of statistical inconsistency (i.e. disagreement between the different sources of evidence) in the data we will employ both local and global approaches [49]. Specifically, we will use the loop-specific approach [50] to detect loops of evidence that might present important inconsistency as well as the node-splitting approach [51] to detect comparisons for which direct estimates disagree with indirect evidence from the entire network. Global methods investigate the presence of inconsistency jointly from all possible sources in the network. For this purpose, we will use the design-by-treatment interaction

model and the I^2 statistic [52, 53].

Subgroup and sensitivity analyses

In case of possible important heterogeneity or inconsistency, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses are planned for hypertensive status, comorbidities, study length (shorter vs. longer-term), sample size, age and sex. Sensitivity analyses are planned for diastolic and systolic blood pressure by analysing only studies considered being at low risk of bias.

Small study effects and publication bias

We will use the comparison-adjusted funnel plot [45] to assess the presence of small-study effects in the network and contour-enhanced funnel plots [54] to investigate whether funnel plot asymmetry is likely to be explained by publication bias.

We will fit all analyses described in a frequentist framework using Stata [55] (*network* package [56]) and we will produce presentation tools with the *network graphs* package [57].

In case that publication bias will be detected we will attempt to fit a selection model that models the relationship between relative effects and probability of a study for being published and we will obtain relative effects 'adjusted' for the impact of publication bias [58].

Quality of the evidence

We will first use our recently developed NutriGrade-tool to evaluate and judge the meta-evidence for pairwise comparisons, which has been especially developed for nutrition research to address specific requirements for this research field [59]. Then, to infer about the quality of evidence from the network meta-analysis, we will combine our judgement about the direct comparisons with their contributions in the estimation within the network as described by Salanti et al. [49].

Discussion

According to the Global Burden of Disease Group in 2012, unhealthy diet is the leading risk factor for premature death and disability [60]. Given the high prevalence and incidence of hypertension and the potential impact of diet, the conduct of the present systematic review with network meta-analysis is of high clinical and practical relevance. This network meta-analysis will be one of the first to compare the direct and indirect effects of different dietary approaches in the management of hypertension and pre-hypertension. The results of the present network meta-analyses will influence evidence-based treatment decision-making, since it will be fundamental for reliable recommendations in the management of hypertension and pre-hypertension.

Declarations

Additional file 1: PRISMA-P checklist

Abbreviations: Not applicable

Competing interests: The authors declare that they have no competing interests.

Consent for publication: Not applicable

Ethics approval and consent to participate: Not applicable

Availability of supporting data: Not applicable

Funding: No funding to declare

Acknowledgements: Not applicable

Authors' information: Not applicable

Authors' contributions: LS, AC, HB, GH contributed to the conception and design of the systematic review and meta-analysis. LS, AC, HB, will be involved in the acquisition and analysis of the data. LS, AC, CS, HB, will interpret the results. LS, AC, GH, CS, HB, drafted this protocol. All authors provided critical revisions of the protocol and approved submission of the final manuscript.

315

References

1. Whelton PK: **Epidemiology of hypertension**. *Lancet* 1994, **344**(8915):101-106.
2. **World Health Organization (2012): Raised Blood Pressure: Situation and Trends. Global Health Observatory http://www.who.int/gho/ncd/risk factors/blood pressure prevalence/en/ (accessed 04.02.2016)**.
3. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW *et al*: **AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation**. *Circulation* 2011, **124**(22):2458-2473.
4. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE *et al*: **2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**. *Circulation* 2014, **129**(25 Suppl 2):S76-99.
5. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM: **Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association**. *Hypertension* 2006, **47**(2):296-308.
6. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH: **Implications of small reductions in diastolic blood pressure for primary prevention**. *Arch Intern Med* 1995, **155**(7):701-709.
7. Staessen JA, Li Y, Thijs L, Wang JG: **Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials**. *Hypertens Res* 2005, **28**(5):385-407.
8. Cornelissen VA, Smart NA: **Exercise training for blood pressure: a systematic review and meta-analysis**. *J Am Heart Assoc* 2013, **2**(1):e004473.
9. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L: **Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(12):1253-1261.
10. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ: **Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. *Adv Nutr* 2016, **7**(1):76-89.
11. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ: **Effect of lower sodium intake on health: systematic review and meta-analyses**. *BMJ* 2013, **346**:f1326.
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement**. *Systematic reviews* 2015, **4**(1):1.
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati AD, Petticrew M, Shekelle P, Stewart LA, the P-PG: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation**. *BMJ* 2015, **349**:g7647.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP *et al*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of**

health care interventions: checklist and explanations. *Ann Intern Med* 2015, **162**(11):777-784.

15. Chaimani A, ., Salanti G, . : **Available from: http://cmimg.cochrane.org/sites/cmimg.cochrane.org/files/uploads/Protocol%20for%20Cochrane%20Reviews%20with%20Multiple%20Interventions.pdf (accessed: 20.01.2016)**.
16. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E: **Dietary advice for reducing cardiovascular risk**. *Cochrane Database Syst Rev* 2013, **12**:CD002128.
17. Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, Stranges S: **'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease**. *Cochrane Database Syst Rev* 2013, **8**:CD009825.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A *et al*: **2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**. *Eur Heart J* 2013, **34**(28):2159-2219.
19. Group TSR: **A Randomized Trial of Intensive versus Standard Blood-Pressure Control**. *New England Journal of Medicine* 2015, **373**(22):2103-2116.
20. Huang PL: **A comprehensive definition for metabolic syndrome**. *Disease Models & Mechanisms* 2009, **2**(5-6):231-237.
21. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM *et al*: **A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group**. *N Engl J Med* 1997, **336**(16):1117-1124.
22. Forman JP, Stampfer MJ, Curhan GC: **Diet and lifestyle risk factors associated with incident hypertension in women**. *JAMA : the journal of the American Medical Association* 2009, **302**(4):401-411.
23. Schwingshackl L, Hoffmann G: **Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(9):929-939.
24. Schwingshackl L, Hoffmann G: **Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies**. *Int J Cancer* 2014, **135**(8):1884-1897.
25. Schwingshackl L, Missbach B, Konig J, Hoffmann G: **Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis**. *Public Health Nutr* 2015, **18**(7):1292-1299.
26. Schwingshackl L, Hoffmann G: **Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies**. *Cancer Med* 2015, **4**(12):1933-1947.
27. Schwingshackl L, Hoffmann G: **Does a Mediterranean-Type Diet Reduce Cancer Risk?** *Curr Nutr Rep* 2016, **5**:9-17.
28. Schwingshackl L, Hoffmann G: **Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis**. *J Acad Nutr Diet* 2013, **113**(12):1640-1661.
29. Schwingshackl L, Hoffmann G: **Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis**. *Nutr J* 2013, **12**:48.

30. Schwingshackl L, Hoffmann G: **Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis**. *Br J Nutr* 2014, **111**(12):2047-2058.
31. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y: **Vegetarian diets and blood pressure: a meta-analysis**. *JAMA Intern Med* 2014, **174**(4):577-587.
32. Jonsson T, Granfeldt Y, Ahren B, Branell UC, Palsson G, Hansson A, Soderstrom M, Lindeberg S: **Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study**. *Cardiovascular diabetology* 2009, **8**:35.
33. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG *et al*: **Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group**. *N Engl J Med* 2001, **344**(1):3-10.
34. Schwingshackl L, Hoffmann G: **Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis**. *Nutr Metab Cardiovasc Dis* 2013, **23**(8):699-706.
35. Schwingshackl L, Missbach B, Dias S, Konig J, Hoffmann G: **Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis**. *Diabetologia* 2014, **57**(9):1789-1797.
36. Schwingshackl L, Dias S, Strasser B, Hoffmann G: **Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: a systematic review and network meta-analysis**. *PLoS One* 2013, **8**(12):e82853.
37. Kessler T, Vilne B, Schunkert H: **The impact of genome-wide association studies on the pathophysiology and therapy of cardiovascular disease**. *EMBO molecular medicine* 2016, **8**(7):688-701.
38. North BJ, Sinclair DA: **The intersection between aging and cardiovascular disease**. *Circulation research* 2012, **110**(8):1097-1108.
39. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC *et al*: **Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program**. *JAMA* 2002, **288**(15):1882-1888.
40. Law M, Wald N, Morris J: **Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy**. *Health Technol Assess* 2003, **7**(31):1-94.
41. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration**. *BMJ* 2009, **339**:b2700.
42. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine* 2009, **6**(7):e1000097.
43. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *BMJ* 2011, **343**:d5928.

44. **Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.** .
45. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G: **Graphical tools for network meta-analysis in STATA**. *PLoS One* 2013, **8**(10):e76654.
46. Krahn U, Binder H, Konig J: **A graphical tool for locating inconsistency in network meta-analyses**. *BMC Med Res Methodol* 2013, **13**:35.
47. Salanti G, Ades AE, Ioannidis JP: **Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial**. *J Clin Epidemiol* 2011, **64**(2):163-171.
48. Riley RD, Higgins JP, Deeks JJ: **Interpretation of random effects meta-analyses**. *BMJ* 2011, **342**:d549.
49. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP: **Evaluating the quality of evidence from a network meta-analysis**. *PLoS One* 2014, **9**(7):e99682.
50. Bucher HC, Guyatt GH, Griffith LE, Walter SD: **The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials**. *J Clin Epidemiol* 1997, **50**(6):683-691.
51. Dias S, Welton NJ, Caldwell DM, Ades AE: **Checking consistency in mixed treatment comparison meta-analysis**. *Stat Med* 2010, **29**(7-8):932-944.
52. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR: **Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies**. *Res Synth Methods* 2012, **3**(2):98-110.
53. Jackson D, Barrett JK, Rice S, White IR, Higgins JP: **A design-by-treatment interaction model for network meta-analysis with random inconsistency effects**. *Stat Med* 2014, **33**(21):3639-3654.
54. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L: **Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry**. *J Clin Epidemiol* 2008, **61**(10):991-996.
55. **StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP**.
56. **White IR. Network meta-analysis. Stata Journal 2015**.
57. **Chaimani, Salanti. Visualizing assumptions and results in network meta-analysis: the network graphs package. Stata Journal 2015.**
58. Mavridis D, Welton NJ, Sutton A, Salanti G: **A selection model for accounting for publication bias in a full network meta-analysis**. *Statistics in medicine* 2014, **33**(30):5399-5412.
59. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopanteils E, Iqbal K *et al*: **Perspective: NutriGrade: A Scoring System to Assess and Judge the Meta-Evidence of Randomized Controlled Trials and Cohort Studies in Nutrition Research**. *Advances in Nutrition: An International Review Journal* 2016, **7**(6):994-1004.
60. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M *et al*: **A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**(9859):2224-2260.

Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

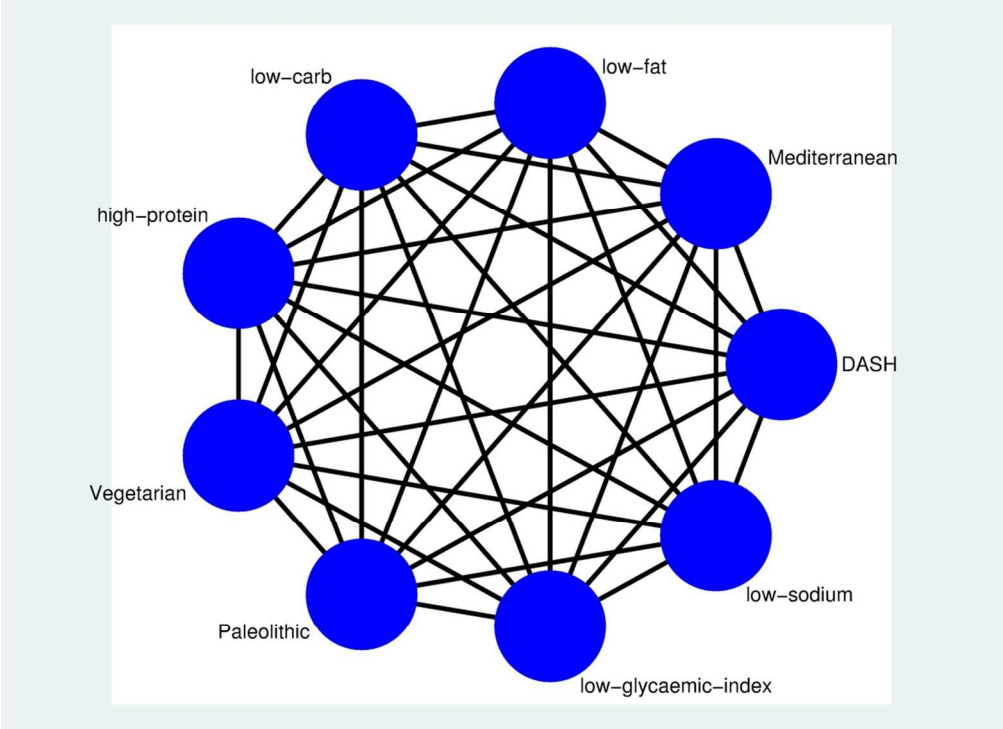

Figure 1: Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

101x73mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐x	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐x	☐	47
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐x	☐	7-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐x	☐	299-303
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐x	☐	296
Sponsor	5b	Provide name for the review funder and/or sponsor	☐x	☐	296
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐x	☐	292

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐x	☐	60-78
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐x	☐	79-88
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐x	☐	96-148
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐x	☐	160-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐x	☐	160-178
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐x	☐	179-188
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐x	☐	179-188
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐x	☐	188-196
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐x	☐	188-196
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐x	☐	150-159
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐x	☐	197-208
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐x	☐	216-244

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐x	☐	216-244
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐x	☐	260-266
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐x	☐	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐x	☐	266-270
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐x	☐	272-278

BMJ Open

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014736.R3
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2017
Complete List of Authors:	Schwingshackl, Lukas Chaimani, Anna; Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina Hoffmann, Georg; Department of Nutritional Sciences, University of Vienna Schwedhelm, Carolina; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE) Boeing, Heiner; German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE)
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, NUTRITION & DIETETICS, PREVENTIVE MEDICINE

Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis

Lukas Schwingshackl[1], Anna Chaimani[2], Georg Hoffmann[3], Carolina Schwedhelm[1], Heiner Boeing[1]

[1] German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

[2] Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Medical School Campus, University of Ioannina, 45110 Ioannina, Greece

[3] Department of Nutritional Sciences, University of Vienna, Althanstraße 14, 1090 Vienna, Austria

Corresponding author: Lukas Schwingshackl, PhD
Arthur-Scheunert-Allee 114-116; 14558 Nuthetal, Germany
T: +49 (0)33200 88-2712
lukas.schwingshackl@dife.de

Email: anna.chaimani@gmail.com
georg.hoffmann@univie.ac.at
carolina.schwedhelm@dife.de
boeing@dife.de

Abstract

Introduction: Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association, all patients with hypertension should adopt the following dietary advices: increased consumption of fresh fruits, vegetables, low-fat dairy products, and sodium reduction. The aim of the present study is to assess the efficacy of different dietary approaches on systolic and diastolic blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and Analysis: We will conduct searches in Cochrane Central Register of Controlled Trials in the Cochrane Library, PubMed, and Google Scholar until November 2016. Citations, abstracts, and relevant papers will be screened for eligibility by two reviewers independently. Randomized trials will be included if they meet the following criteria: (1) hypertension (as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) or high normal blood pressure (mean systolic blood pressure ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), (2) years of age: ≥18, (3) Intervention diets (different type of dietary approaches: e.g. Dietary Approach to Stop Hypertension diet; Mediterranean diet, Vegetarian diet, Paleolithic diet, low sodium diet) either hypo-, iso-caloric, or ad libitum diets, (4) intervention period ≥12 weeks. For each outcome measure of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values (or change scores). Subgroup analyses are planned for: hypertensive status, study length, sample size, age, and sex.

Ethics and Dissemination: As this study is based solely on the published literature, no ethics approval is required. We will publish our network meta-analysis in a peer-reviewed scientific journal.

Systematic Review Registration: PROSPERO: CRD42016049243

Keywords: diet, hypertension, blood pressure, network meta-analysis, evidence synthesis, systematic review

Strengths and limitations of this study

- The protocol addresses the important question of which dietary approach offers the most benefits in the management of elevated blood pressure
- The present network meta-analysis has a clearly established aim, stringent inclusion criteria, state of the art methods for data collection, and quantitative and qualitative synthesis
- Limitations include variations in trial design and regimen, adherence to dietary protocols, lack of blinding across the included intervention trials, and ecological fallacy

Background

Due to its frequent occurrence and high impact on the development of cardiovascular and kidney disease, hypertension is one of the most challenging problems adversely affecting public-health worldwide [1]. The prevalence of hypertension accounts for nearly 40% of people older than 25 years worldwide, and the number of patients has increased from 600 million to a billion in 2008 [2].

Lifestyle modification is one of the cornerstones of the management of hypertension. According to the most recent guidelines by the American Heart Association and the European Society of Cardiology and Hypertension, all patients with hypertension should follow dietary modifications: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction [3, 4].

Accumulating evidence indicates that dietary factors have a predominant role in the management of elevated blood pressure [5]. In individuals without hypertension dietary changes reduce blood pressure and prevent hypertension, thereby lowering the risk of blood pressure-related complications. Epidemiological studies suggest that even slight reductions in blood pressure will reduce the risk of cardiovascular disease [6, 7].

Whereas it is already well established that aerobic exercise is more effective in reducing blood pressure in hypertensive patients compared to resistance training [8], the question regarding the most effective dietary approach in the treatment of hypertension and high normal pressure has not been evaluated.

To our knowledge, no up-to-date systematic review and network meta-analysis has been conducted to compare different dietary modifications in the management of hypertension and high normal blood pressure. Some pairwise meta-analyses have been published comparing DASH dietary approaches [9], combined dietary approaches [10], and lower sodium intake vs usual care/control diet [11]. One of the most important questions that remain to be answered

is which dietary approach offers the most benefits in the management of elevated blood pressure.

Therefore, our aim is to compare the efficacy of different dietary approaches on blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomized trials.

Methods and design

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016049243). The present systematic review protocol was planned, conducted, and reported in adherence to standards of quality for reporting systematic reviews and network meta-analysis protocols [12-15] (additional file 1).

Eligibility criteria

Studies will be included in the meta-analysis if they meet all of the following criteria:

Types of studies

Randomized trial design comparison between different dietary approaches (e.g. Dietary Approach to Stop Hypertension; Mediterranean diet; Vegetarian diet; Palaeolithic diet; low sodium diet; low fat diet; low carbohydrate diet; high protein diet; low glycaemic index/load diet) with a minimum intervention period of 3 months according to recent Cochrane Reviews on diet and cardiovascular risk [16, 17]. If randomized trials have more than one different length of outcomes (e.g. 12 weeks and 12 months), we will include the long-term data.

Types of participants

We will consider only adults with a mean age ≥18 years. Hypertension was defined according to the European Society of Cardiology and European Society of Cardiology & Hypertension as mean values ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure. Moreover, all patients taking antihypertensive medication will be included [18].

High normal blood pressure (mean systolic blood pressure ≥130 mmHg and/or mean diastolic blood pressure ≥85 mmHg), was also defined according to the European Society of Cardiology & Hypertension and the recently published SPRINT trial [18, 19]. Including patients with high normal blood pressure is of major relevance since it is part of the metabolic syndrome diagnosis criteria [20].

Types of Interventions

Accumulating evidence indicates that dietary factors play an important role in the treatment of elevated blood pressure. Likewise, dietary modifications decrease blood pressure [21] and reduce the risk of hypertension in people without established high blood pressure [22]. Even if modest, a reduction in blood pressure can have an important impact on the health of entire populations [5]. We will include all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets (direct evidence).

Eligible types of dietary approaches will be as follows:

- Dietary Approach to Stop Hypertension (DASH): high intake of fruits & vegetables, low-fat dairy, whole grains [21]
- Mediterranean dietary pattern: olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals [23-27]
- Low carbohydrate diet (<30% of the total energy intake from carbohydrates, high intake of animal or/and plant protein) [28]
- High protein diet [29] (≥ 25% of total energy intake from protein)
- Low fat diet (<30% of total energy intake from fat, high in grains and cereals) [28, 30]
- Vegetarian diet (no meat or fish) [31]
- Palaeolithic diet (lean meat, fish, eggs, vegetables, fruits, berries, and nuts; dairy products, cereals, added salt, and refined fats and sugar were excluded) [32]
- Low sodium diet [33]
- Low glycaemic index/load diet [34]

Either energy-restricted diets, iso-caloric, or ad libitum diets will be considered.

The following types of RCTs will be excluded:

- Intervention studies solely based on dietary supplements (e.g. vitamin C, vitamin E, calcium, potassium, garlic, soy protein) or single foods (e.g. nuts);
- Placebo used in any form of dietary supplements (e.g. potassium);
- Studies with an exercise/medication [35, 36] co-intervention that was not applied in all of the intervention/control groups;
- Interventions based on very low energy diets (i.e. <600 kcal/day)

Figure 1 shows the network of possible pairwise comparisons between the eligible dietary interventions. If we identify a study that combines low sodium and a low fat diet (and does not fulfil the criteria of a DASH diet), we will handle this study as evaluating a different dietary regimen (low fat + low sodium) in the network meta-analysis. If food-based interventions fulfil also the criteria of a nutrient-based dietary regimen, we will perform sensitivity analysis for food-based vs. nutrient-based dietary regimen taking into account possible overlaps.

Outcome measures

Although cardiovascular diseases are determined by variables that cannot be influenced, such as age or heritability [37, 38], there are several predictors for CVD that can be affected by lifestyle improvements. As mentioned above, blood pressure is the most important of these modifiable risk factors. Epidemiological studies show that a reduction of approximately 3 mmHg in systolic blood pressure has been estimated to reduce risks of CHD by 5–9%, stroke by 8–14%, and all-cause mortality by 4% [39]. Lowering diastolic blood pressure by 5 mmHg reduces the risk of stroke by 32%, and ischemic heart disease by an estimated 20% [40].

Several other systematic reviews and pairwise meta-analyses have included systolic and diastolic blood pressure as outcomes [9, 10]. In order to achieve a better comparability

between the data compiled by different studies, the patients should ideally hold a sitting position for 3-5 minutes prior to blood pressure measurement [18].

Search strategy

The search will be performed by LS and CS, and differences resolved by discussion with a third reviewer (HB). We will conduct searches in PubMed, Cochrane CENTRAL, and google scholar. We will search for articles of original research by using the following search terms:

#1 diet [MeSH Terms]

#2 low carbohydrate OR high carbohydrate OR low fat OR high fat OR low protein OR high protein OR vegetarian OR vegan OR Mediterranean OR DASH OR dietary approaches to stop hypertension OR low glycaemic index OR low glycaemic load OR Palaeolithic OR low-calorie OR atkins OR low sodium

#3 blood pressure OR hypertension OR diastolic OR systolic

#4 random* NOT animals

#5 (#1 AND #2 AND #3 AND #4)

Moreover, the reference lists from the retrieved articles, systematic reviews and meta-analyses will be checked to search for further relevant studies (umbrella review of systematic reviews and meta-analyses). There will be no restrictions on language or publication year. Studies published in languages other than English will be translated by international scientists in our institute.

Study selection process

Two reviewers will independently screen titles and abstracts of all the retrieved bibliographic records. Full texts of all potentially eligible records passing the title and abstract screening level will be retrieved and examined independently by two reviewers (for each database) with the above mentioned eligibility and exclusion criteria [41, 42]. Disagreements will be resolved by consensus or adjudication of another author. A flow-diagram will outline the study selection process and reasons for exclusions. If a study is published in duplicate, we

will include the version containing the most comprehensive information (e.g. longest follow-up duration and/or largest number of study participants).

Data extraction

The following data will be extracted from each study: first author's last name, publication year, country of origin, study design (randomized trial or cross-over trial), study length, number of arms, participants' sex and age (effect modifier), sample size, diagnostic criteria for hypertension, mean baseline systolic and diastolic blood pressure, mean baseline BMI, method of blood pressure ascertainment, body weight (effect modifier), medication intake (predominately antihypertensive drugs), dietary protocols, dietary assessment method, any physical activity details, participant health status (diabetes mellitus type 2, coronary artery disease, alcohol intake, smoking), specification of the control group (if available), and where reported: drop-outs, and funding source.

Risk of bias assessment

Full copies of the studies will be independently assessed by two authors for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration [43]. The following sources of bias will be assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Randomized controlled trials in nutrition research are often prone to inherent methodological constraints. For example, they sometimes cannot be controlled with "true" placebos, but rather by a limitation of certain aspects of nutrient composition, food groups or dietary patterns.

Studies will be classified as being at high risk of bias if achieving fewer than four out of a maximum yield of five items at low risk of bias using the risk of bias assessment tool from the Cochrane Collaboration.

Dealing with missing data

We will try to obtain relevant missing data from authors of the included randomized trials (by e-mail). If the post-intervention values with the corresponding standard deviations are not available, the change scores with the corresponding standard deviations will be imputed, according to the guidelines of the Cochrane Handbook [44].

Evaluation of synthesis assumptions

Data synthesis

Description of the available data

Descriptive statistics for study and population characteristics describing the available data and selected variables (e.g. age, study length, outcome-relevant baseline risk factors, etc.) will be generated for each pairwise comparison. We will present the available direct comparisons between different dietary interventions and control groups using a network diagram for each outcome [45]. The size of the nodes (circles) will be proportional to the sample size of each dietary intervention and the thickness of the edges (lines) proportional to the number of studies available. We will also use the contribution matrix to identify the direct comparisons with greater influence on the network relative effects [45, 46].

Standard pairwise meta-analyses and network meta-analyses

For each outcome of interest, random effects pairwise and network meta-analyses will be performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the post-intervention values or the changes from baseline scores of the different dietary interventions. Intention-to-treat analysis data will be used when it is available. Separate pairwise meta-analyses will be used first to compare all the interventions with available direct evidence. Heterogeneity between trial results will be measured using the I^2-statistic; I^2 >50% will be considered to represent substantial heterogeneity. Forest plots will be generated to illustrate the study-specific effect sizes along

with a 95% CI. Network meta-analysis will be then used to synthesize all the available evidence. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomization of individual trials. We will perform a random effects network meta-analysis for each outcome to estimate all possible pairwise relative effects and obtain a clinically meaningful relative ranking of the different dietary interventions. Multi-arm trials will be modeled properly accounting for the correlation of the effect sizes from such studies. We will present summary mean differences in a league table. We will also estimate the relative ranking of the different diets for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA) [47]. For each outcome we will assume a common network-specific heterogeneity parameter and we will estimate the predictive intervals to assess how much this heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies [48]. We will fit all analyses described in a frequentist framework using Stata [49] (*network* package [50]) and we will present our results with the *network graphs* package [51].

Assumption of transitivity

Transitivity is the fundamental assumption of indirect comparisons and network meta-analysis, and its violation threatens the validity of the findings obtained from a network of studies. We plan on including changes in body weight and mean baseline age as potential effect modifiers.

Assessment of inconsistency

To evaluate the presence of statistical inconsistency (i.e. disagreement between the different sources of evidence) in the data we will employ both local and global approaches [52]. Specifically, we will use the loop-specific approach [53] to detect loops of evidence that might present important inconsistency as well as the node-splitting approach [54] to detect

comparisons for which direct estimates disagree with indirect evidence from the entire network. Global methods investigate the presence of inconsistency jointly from all possible sources in the network. For this purpose, we will use the design-by-treatment interaction model and the I^2 statistic [55, 56].

Subgroup and sensitivity analyses

In case of possible important heterogeneity or inconsistency, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses are planned for hypertensive status, comorbidities, study length (shorter vs. longer-term), sample size, age, and sex. Sensitivity analyses are planned for diastolic and systolic blood pressure by analysing only studies considered being at low risk of bias.

Small study effects and publication bias

We will use the comparison-adjusted funnel plot [45] to assess the presence of small-study effects in the network and contour-enhanced funnel plots [57] to investigate whether funnel plot asymmetry is likely to be explained by publication bias.

In case that publication bias will be detected we will attempt to fit a selection model that represents the relationship between relative effects and probability of a study for being published and we will obtain relative effects 'adjusted' for the impact of publication bias [58].

Quality of the evidence

We will first use our recently developed NutriGrade-tool to evaluate and judge the meta-evidence for pairwise comparisons, which has been especially developed for nutrition research to address specific requirements for this research field [59]. Then, to infer about the quality of evidence of the network meta-analysis, we will combine our judgement about the direct comparisons and their individual contribution to the estimates within the network as described by Salanti et al. [52].

Discussion

According to the Global Burden of Disease Group in 2012, unhealthy diet is the leading risk factor for premature death and disability [60]. Given the high prevalence and incidence of hypertension and the potential impact of diet, the conduct of the present systematic review with network meta-analysis is of high clinical and practical relevance. This network meta-analysis will be one of the first to compare the direct and indirect effects of different dietary approaches in the management of hypertension and pre-hypertension. The results of the present network meta-analysis will influence evidence-based decision-making in treatment prescription, since it will be fundamental for reliable recommendations in the management of hypertension and pre-hypertension.

Declarations

Additional file 1: PRISMA-P checklist

Abbreviations: Not applicable

Competing interests: The authors declare that they have no competing interests.

Consent for publication: Not applicable

Ethics approval and consent to participate: Not applicable

Availability of supporting data: Not applicable

Funding: No funding to declare

Acknowledgements: Not applicable

Authors' information: Not applicable

Authors' contributions: LS, AC, HB, GH contributed to the conception and design of the systematic review and meta-analysis. LS, AC, HB, will be involved in the acquisition and analysis of the data. LS, AC, CS, HB, will interpret the results. LS, AC, GH, CS, HB, drafted this protocol. All authors provided critical revisions of the protocol and approved submission of the final manuscript.

References

1. Whelton PK: **Epidemiology of hypertension**. *Lancet* 1994, **344**(8915):101-106.
2. **World Health Organization (2012): Raised Blood Pressure: Situation and Trends. Global Health Observatory http://www.who.int/gho/ncd/risk factors/blood pressure prevalence/en/ (accessed 04.02.2016)**.
3. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW *et al*: **AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation**. *Circulation* 2011, **124**(22):2458-2473.
4. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE *et al*: **2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**. *Circulation* 2014, **129**(25 Suppl 2):S76-99.
5. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM: **Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association**. *Hypertension* 2006, **47**(2):296-308.
6. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH: **Implications of small reductions in diastolic blood pressure for primary prevention**. *Arch Intern Med* 1995, **155**(7):701-709.
7. Staessen JA, Li Y, Thijs L, Wang JG: **Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials**. *Hypertens Res* 2005, **28**(5):385-407.
8. Cornelissen VA, Smart NA: **Exercise training for blood pressure: a systematic review and meta-analysis**. *J Am Heart Assoc* 2013, **2**(1):e004473.
9. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L: **Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(12):1253-1261.
10. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ: **Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. *Adv Nutr* 2016, **7**(1):76-89.
11. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ: **Effect of lower sodium intake on health: systematic review and meta-analyses**. *BMJ* 2013, **346**:f1326.
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement**. *Systematic reviews* 2015, **4**(1):1.
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati AD, Petticrew M, Shekelle P, Stewart LA, the P-PG: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation**. *BMJ* 2015, **349**:g7647.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP *et al*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of**

health care interventions: checklist and explanations. *Ann Intern Med* 2015, **162**(11):777-784.

15. Chaimani A, ., Salanti G, . : **Available from: http://cmimg.cochrane.org/sites/cmimg.cochrane.org/files/uploads/Protocol%20for%20Cochrane%20Reviews%20with%20Multiple%20Interventions.pdf (accessed: 20.01.2016)**.
16. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E: **Dietary advice for reducing cardiovascular risk**. *Cochrane Database Syst Rev* 2013, **12**:CD002128.
17. Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, Stranges S: **'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease**. *Cochrane Database Syst Rev* 2013, **8**:CD009825.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A *et al*: **2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**. *Eur Heart J* 2013, **34**(28):2159-2219.
19. Group TSR: **A Randomized Trial of Intensive versus Standard Blood-Pressure Control**. *New England Journal of Medicine* 2015, **373**(22):2103-2116.
20. Huang PL: **A comprehensive definition for metabolic syndrome**. *Disease Models & Mechanisms* 2009, **2**(5-6):231-237.
21. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM *et al*: **A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group**. *N Engl J Med* 1997, **336**(16):1117-1124.
22. Forman JP, Stampfer MJ, Curhan GC: **Diet and lifestyle risk factors associated with incident hypertension in women**. *JAMA : the journal of the American Medical Association* 2009, **302**(4):401-411.
23. Schwingshackl L, Hoffmann G: **Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials**. *Nutr Metab Cardiovasc Dis* 2014, **24**(9):929-939.
24. Schwingshackl L, Hoffmann G: **Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies**. *Int J Cancer* 2014, **135**(8):1884-1897.
25. Schwingshackl L, Missbach B, Konig J, Hoffmann G: **Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis**. *Public Health Nutr* 2015, **18**(7):1292-1299.
26. Schwingshackl L, Hoffmann G: **Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies**. *Cancer Med* 2015, **4**(12):1933-1947.
27. Schwingshackl L, Hoffmann G: **Does a Mediterranean-Type Diet Reduce Cancer Risk?** *Curr Nutr Rep* 2016, **5**:9-17.
28. Schwingshackl L, Hoffmann G: **Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis**. *J Acad Nutr Diet* 2013, **113**(12):1640-1661.
29. Schwingshackl L, Hoffmann G: **Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis**. *Nutr J* 2013, **12**:48.

30. Schwingshackl L, Hoffmann G: **Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis**. *Br J Nutr* 2014, **111**(12):2047-2058.
31. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y: **Vegetarian diets and blood pressure: a meta-analysis**. *JAMA Intern Med* 2014, **174**(4):577-587.
32. Jonsson T, Granfeldt Y, Ahren B, Branell UC, Palsson G, Hansson A, Soderstrom M, Lindeberg S: **Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study**. *Cardiovascular diabetology* 2009, **8**:35.
33. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG *et al*: **Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group**. *N Engl J Med* 2001, **344**(1):3-10.
34. Schwingshackl L, Hoffmann G: **Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis**. *Nutr Metab Cardiovasc Dis* 2013, **23**(8):699-706.
35. Schwingshackl L, Missbach B, Dias S, Konig J, Hoffmann G: **Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis**. *Diabetologia* 2014, **57**(9):1789-1797.
36. Schwingshackl L, Dias S, Strasser B, Hoffmann G: **Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: a systematic review and network meta-analysis**. *PLoS One* 2013, **8**(12):e82853.
37. Kessler T, Vilne B, Schunkert H: **The impact of genome-wide association studies on the pathophysiology and therapy of cardiovascular disease**. *EMBO molecular medicine* 2016, **8**(7):688-701.
38. North BJ, Sinclair DA: **The intersection between aging and cardiovascular disease**. *Circulation research* 2012, **110**(8):1097-1108.
39. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC *et al*: **Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program**. *JAMA* 2002, **288**(15):1882-1888.
40. Law M, Wald N, Morris J: **Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy**. *Health Technol Assess* 2003, **7**(31):1-94.
41. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration**. *BMJ* 2009, **339**:b2700.
42. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine* 2009, **6**(7):e1000097.
43. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *BMJ* 2011, **343**:d5928.

44. **Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.** .
45. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G: **Graphical tools for network meta-analysis in STATA**. *PLoS One* 2013, **8**(10):e76654.
46. Krahn U, Binder H, Konig J: **A graphical tool for locating inconsistency in network meta-analyses**. *BMC Med Res Methodol* 2013, **13**:35.
47. Salanti G, Ades AE, Ioannidis JP: **Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial**. *J Clin Epidemiol* 2011, **64**(2):163-171.
48. Riley RD, Higgins JP, Deeks JJ: **Interpretation of random effects meta-analyses**. *BMJ* 2011, **342**:d549.
49. **StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP**.
50. **White IR. Network meta-analysis. Stata Journal 2015**.
51. **Chaimani, Salanti. Visualizing assumptions and results in network meta-analysis: the network graphs package. Stata Journal 2015.**
52. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP: **Evaluating the quality of evidence from a network meta-analysis**. *PLoS One* 2014, **9**(7):e99682.
53. Bucher HC, Guyatt GH, Griffith LE, Walter SD: **The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials**. *J Clin Epidemiol* 1997, **50**(6):683-691.
54. Dias S, Welton NJ, Caldwell DM, Ades AE: **Checking consistency in mixed treatment comparison meta-analysis**. *Stat Med* 2010, **29**(7-8):932-944.
55. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR: **Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies**. *Res Synth Methods* 2012, **3**(2):98-110.
56. Jackson D, Barrett JK, Rice S, White IR, Higgins JP: **A design-by-treatment interaction model for network meta-analysis with random inconsistency effects**. *Stat Med* 2014, **33**(21):3639-3654.
57. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L: **Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry**. *J Clin Epidemiol* 2008, **61**(10):991-996.
58. Mavridis D, Welton NJ, Sutton A, Salanti G: **A selection model for accounting for publication bias in a full network meta-analysis**. *Statistics in medicine* 2014, **33**(30):5399-5412.
59. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopanteils E, Iqbal K *et al*: **Perspective: NutriGrade: A Scoring System to Assess and Judge the Meta-Evidence of Randomized Controlled Trials and Cohort Studies in Nutrition Research**. *Advances in Nutrition: An International Review Journal* 2016, **7**(6):994-1004.
60. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M *et al*: **A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**(9859):2224-2260.

Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

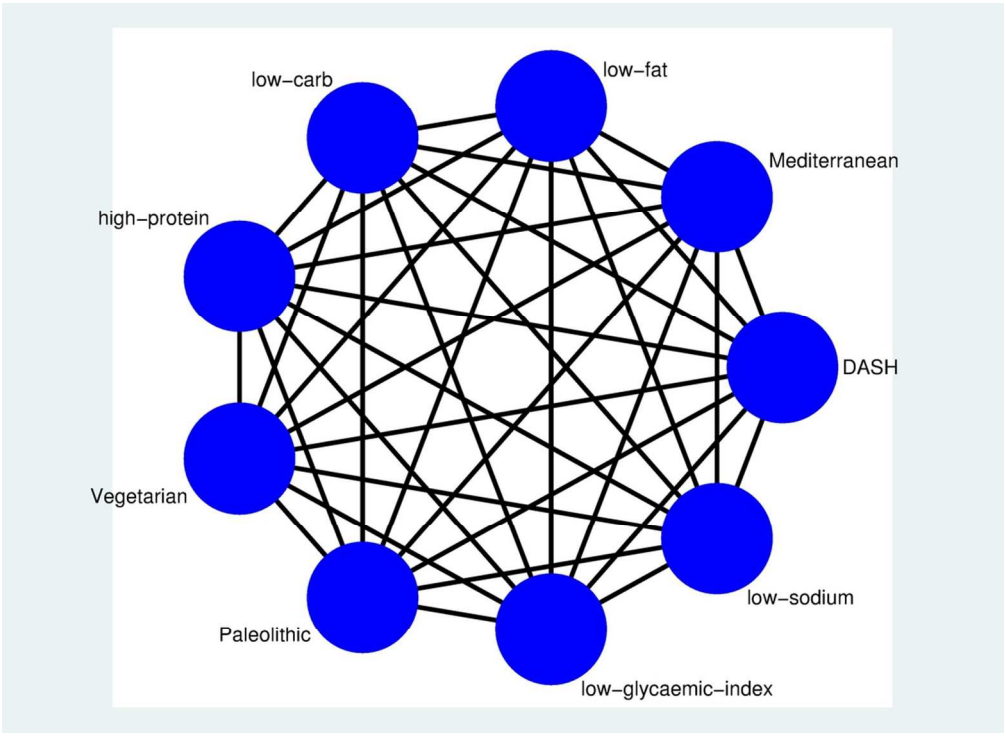

Figure 1: Figure 1. Network of all possible pairwise comparisons between the eligible dietary interventions.

101x73mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P**:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐x	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐x	☐	47
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐x	☐	7-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐x	☐	310-314
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐x	☐	303
Sponsor	5b	Provide name for the review funder and/or sponsor	☐x	☐	303
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐x	☐	303
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☐x	☐	62-80
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐x	☐	81-90
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐x	☐	97-154
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐x	☐	168-184
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐x	☐	168-184
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐x	☐	185-193
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐x	☐	185-193
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐x	☐	185-193
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐x	☐	195-203
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐x	☐	156-167
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐x	☐	204-215
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐x	☐	233-255
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of	☐x	☐	233-255

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		consistency (e.g., I^2, Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐x	☐	256-275
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐x	☐	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐x	☐	276-282
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐x	☐	283-289